INTRAVENOUS INJECTION IN WOUND SHOCK

Intravenous Injection in Wound Shock

BEING THE OLIVER-SHARPEY LECTURES DELIVERED BEFORE THE ROYAL COLLEGE OF PHYSICIANS OF LONDON IN MAY 1918

BY

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Dedicated to

MAJOR-GENERAL CUTHBERT WALLACE

C.M.G., F.R.C.S.

IN APPRECIATION OF HIS WORK ON

WOUND SHOCK AND ITS TREATMENT

TO WHICH THE

INVESTIGATIONS DESCRIBED IN THIS BOOK

OWE WHAT PRACTICAL VALUE THEY POSSESS

PREFATORY NOTE

THE present work consists of an amplification of the subject-matter of the lectures as delivered, an abstract of which has been already published in the *British Medical Journal* of 18th May 1918. A more detailed explanation than was possible in the time available seems desirable, especially as concerns certain questions relating to the production of œdema, and to the so-called "acidosis." Some further evidence that has come to light since the delivery of the lectures has been, as far as possible, incorporated, and a larger number of illustrative cases, experimental and clinical, has been added. The subject itself involves so many physiological processes that a complete discussion is clearly impossible, but the list of papers given at the end of the book will serve, in some degree, to make up this deficiency.

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INTRAVENOUS INJECTION IN WOUND SHOCK

LECTURE I

WOUND SHOCK

THE subject with which I propose to deal in these two lectures is the treatment of that state of depressed activity of the bodily functions which frequently follows upon severe injury, either by wounds received in warfare or in surgical operations, and also after hæmorrhage from any cause. The name "wound shock" was suggested by Cowell (1917, p. 58). It seems to be the most appropriate name, on the whole, although perhaps not quite comprehensive enough. The disturbance of mental functions, sometimes known as "shell shock," is not included in the scope of the present inquiry.

The importance of the problems involved needs no emphasis at the present time.

Although the condition is generally recognised and unmistakable, the primary cause is still obscure, and I do not feel called upon to define or explain what is the actual nature of the conditions underlying it, except to mention that the most obvious signs are a low blood pressure, and the consequences

of the deficient supply of blood to vital organs which results therefrom.

While the primary cause is still unknown, there are some hypotheses which can be definitely excluded and should be briefly alluded to, because their rejection also clears away certain modes of treatment based on them.

The cause of wound shock is *not*—

1. **Acapnia**, meaning by that the state brought about by too great removal of carbon dioxide by violent respiration. This might lead to deficient supply of oxygen, owing to the failure of stimulation of the respiratory centre by the necessary hydrogen-ion concentration, given by the carbon dioxide in the blood. Acapnia might indeed be produced by excessive respiratory efforts in consequence of pain, but the testimony of the most competent observers is that the majority of wounded men do not complain of pain, and this was the impression given me in a visit to some Casualty Clearing Stations in France and Flanders. The most insistent demands are for water and warmth. Moreover, the character of the respiration in shock is usually described as being rapid and *shallow*, not of such a character as to result in increased ventilation of the lungs.

2. **Suprarenal Exhaustion.**—There is found to be an *increase* of adrenaline in the blood in experimental shock (Bedford, 1917), and the work of Cannon and De la Paz (1911), Elliott (1912), and others on the effect of fear and emotions in general would lead us to expect this to be the case when wounds are received in battle.

3. **Exhaustion of Nerve Centres**, especially

of the vaso-motor centre. There is no evidence of paralysis of bulbar centres in the early stages of shock, although prolonged low blood pressure, as we shall see, may lead to it. In shock produced experimentally, it can be shown that the bulbar centres retain a nearly normal excitability for some time after the state has developed. The comparatively brief collapse occurring on incidence of the injury is rather of the nature of a functional inhibition, although it may play a part in the production of the later true shock.

4. **Inefficient Cardiac Contraction.**—That the heart is not weakened is shown by the fact that when blood or gum solution is infused, the blood pressure rises to its normal height. Markwalder and Starling (1913, p. 279) remark that the efficiency of the heart is impaired if the arterial pressure falls below about 90 mm. of mercury, but it recovers completely on raising the pressure again. Presumably the work done under the low pressure is not so great as to result in permanent damage, while the oxygen supply is sufficient for the actual requirement.

5. **Arterial or Venous Paralysis,** especially of the splanchnic vessels. This is mainly identical with No. 3 above. Further evidence is given by the observations of surgeons in abdominal operations, who have carefully looked for signs of distension of arterioles and veins of the splanchnic area, and failed to detect any. It may be mentioned, however, that some caution is needed in drawing conclusions if there has been a large loss of blood, since it is possible that too little may

be in circulation to distend even relaxed vessels appreciably. But in many cases of shock there is reason to believe that little or no hæmorrhage has occurred, although, again, care must be exercised in assuming that this is the case from the state of the dressings on arrival at the Casualty Clearing Station, since they may have been recently changed. The statement made in this paragraph must not be taken as prejudging the question as to the existence of a reflex peripheral vaso-dilatation in the initial stage of wound shock. Such a state may possibly be of importance in starting the vicious circles leading to secondary shock.

The state brought about by simple hæmorrhage is very difficult to distinguish in practice from secondary wound shock, especially since there are very few cases entirely free from more or less loss of blood. Fortunately, however, as we shall see later, the treatment is practically the same for both. The view that has most evidence in its favour at present is that in both states there is loss of blood from currency, and Cannon (1917, p. 81) has suggested the name *exæmia* to express this conception. Where the blood has gone to in cases where little has been lost externally is still a matter of uncertainty, but various facts, to be referred to below, point to its being held up by stasis in the capillary districts of certain parts of the body. We see then, at the outset, that the condition to be relieved is one of loss of blood, either actually out of the body altogether, or held up somewhere out of circulation.

This is the state known as secondary wound shock, as distinct from the primary collapse and fall

of pressure which may result immediately on receipt of an injury. Captain Kenneth Walker has pointed out the beneficial effect of this latter fall of pressure in tending to lessen loss of blood.

Since it is the secondary state that is the serious one requiring treatment, the diagram of Fig. 1, which is a combination of two diagrams given by Cowell (1917, pp. 62 and 64), may assist in distinguishing the two states, although the one may insensibly pass into the other. One of four things may happen after a wound has been received. Taking the blood pressure as an index, this may remain unaltered, with absence of shock altogether. The other extreme is rapid death with fall to zero. It may, however, fall rapidly to a somewhat low level, and then recover by warmth and rest during transit to the Casualty Clearing Station, so that no secondary shock develops. On the other hand, after partial recovery, secondary shock may come on, so that, on arrival, the blood pressure has fallen again to a low level, with the other frequently described symptoms of pallor, coldness, and so on. Or the primary shock may pass gradually into secondary shock without any intervening recovery. The fourth possibility is a gradual development of secondary shock without the manifestation of primary shock. During the journey to the Casualty Clearing Station this may improve, remain stationary, or become progressively more pronounced, with continued fall of blood pressure until death.

The chief object of these lectures is to discuss how this fall of blood pressure, the most serious aspect of shock, can most effectively be brought to

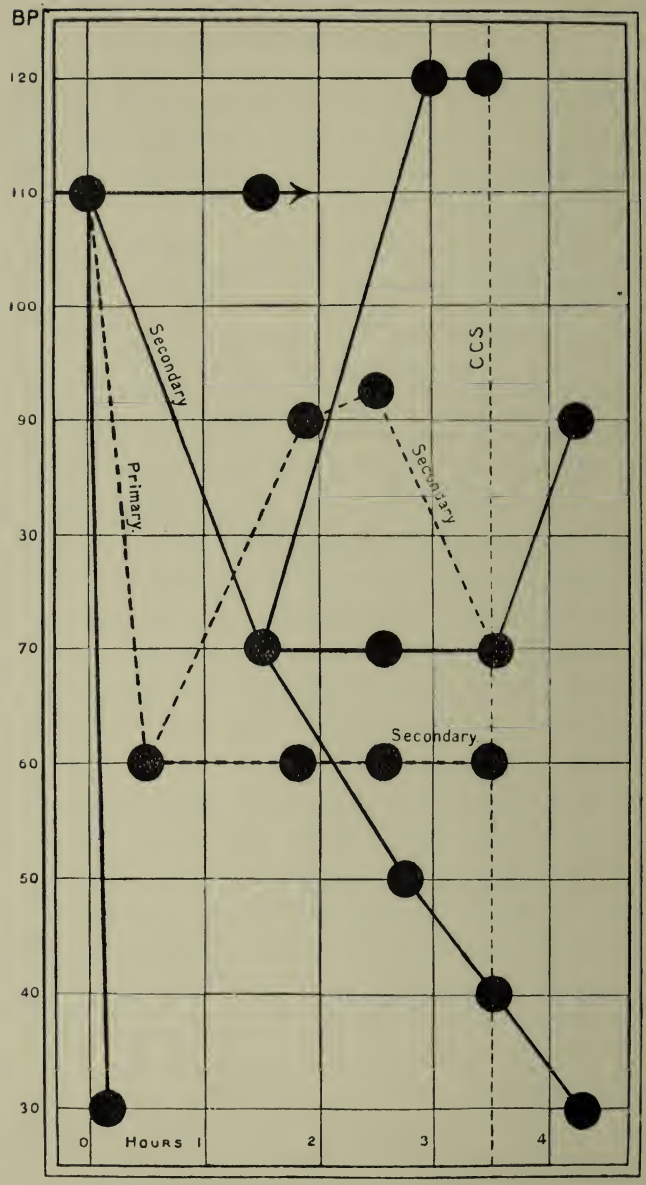

Fig. 1.—Diagram (after Cowell, 1917, pp. 62 and 64) to illustrate the various **ways in which Wound Shock may come on.**

The arterial pressure is taken as the criterion of the severity or the effect, and is given by the ordinates in mm. of mercury. The time of arrival at the Casualty Clearing Station is marked for comparison by the vertical dotted line, but of course it varies greatly in individual cases.

a normal level. I venture to think that the subject is one eminently appropriate to the memory of their founder, who devoted so much valuable work to the methods of measuring blood pressure in man, and repeatedly insisted in his writings on the clinical importance of such measurements. His valuable book on "Studies in Blood Pressure" may be especially mentioned here.

We may first consider shortly why a low blood pressure is so injurious as to demand the use of means to raise it. There are two aspects to be taken account of:—

1. The effects of the low blood pressure itself.

2. The exaggeration of the effects of other injurious factors, themselves tending to lower the blood pressure, but not necessarily serious unless combined with even comparatively small loss of blood; or vice versa, an unimportant loss of blood may become serious when combined with one or more of these other factors.

1. The Direct Effects of a Low Blood Pressure.

To avoid misunderstanding, it should be pointed out at once that a high arterial pressure is not to be looked upon as the end in itself. The object is to ensure an adequate supply of blood to the various organs of the body, and the most important and vital constituent of the blood is oxygen, since oxygen is used up rapidly and in large amount. It is not merely that the tissue cells cease to perform their functions in the absence of oxygen, to resume them again in a normal manner when the supply

recommences, but that their metabolism changes to one which may be of an injurious nature, while structural alterations of a pathological kind take place, often of an irreparable nature.

The Rate of Blood Flow through an organ is not directly proportional to the blood pressure. Thus Gesell (1918) has shown that a reduction of arterial pressure from 124 mm. to 84 mm. of mercury (a reduction to two-thirds) reduces the blood flow through the submaxillary gland to one-sixth of its value. An important point is also that a small fall from the normal height has a greater effect than a similar further fall from a lower height. Thus, a fall from 84 to 54 mm. caused a reduction of 10 per cent. in the rate of flow, whereas the numbers given above amount to a reduction of more than 50 per cent. for a fall from 124 to 94 mm. In some experiments in which I recorded the rate of flow from the deep femoral vein of a cat, the nerves of the leg being cut in order to avoid vaso-motor reflexes, the number of drops per minute at an arterial pressure of 66 mm. was 60, at a pressure of 54 mm. it was 40 (see Fig. 2). That is, while the blood pressure fell by 18 per cent., the rate of blood flow fell by 33 per cent. These different pressures were the top and bottom of Traube-Hering waves, and these followed one another at about two to three minute intervals, so that the absence of disturbing factors was ensured. The results are not so striking as those of Gesell, but of the same significance from the practical point of view, namely, that it is a matter of importance to replace even a comparatively small loss of blood,

or to improve what might be supposed to be a fall of pressure of no particular consequence.

Renal Secretion.—The kidney plays an important part in the elimination of acid products and toxic substances from the blood. It is well known how great is the dependence of its activity on the arterial blood pressure.

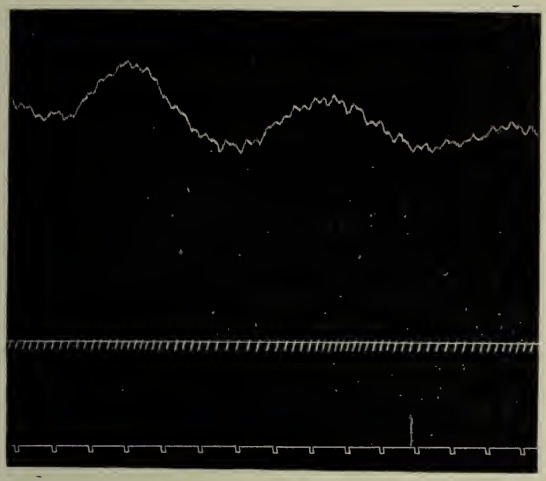

FIG. 2.—**Blood Flow through Leg of Cat as affected by Changes of Arterial Pressure.**

Nerves cut. The waves in the blood pressure curve (top tracing) were spontaneous. The middle line marks each drop of blood falling from the deep femoral vein. The time tracing at the bottom marks each ten seconds.

Pathological Changes in the Cells of various organs have been described as results of low blood pressure. The effect of a short anæmia in producing a long-lasting cessation of renal activity is familiar. Some experiments made by Dr Jonescu (1909) with me, on the stimulation of salivary centres by asphyxia, showed that want of oxygen,

whether due to deficiency in the air breathed or to a low blood pressure from hæmorrhage, caused a rapid decrease in the rate of secretion. Fig. 3 illustrates the effect of the latter. Markwalder and Starling (1913) showed that, when the pressure in

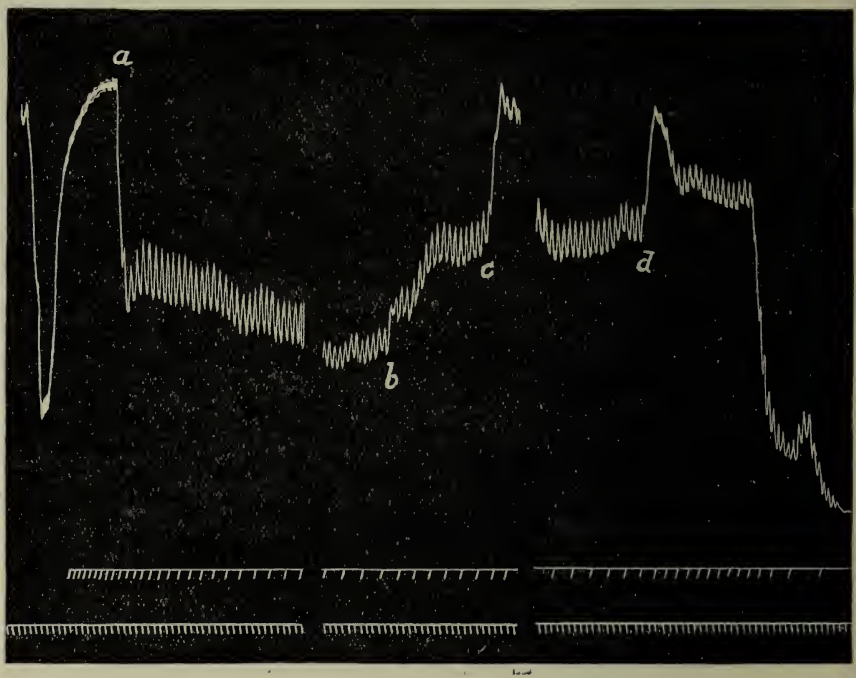

FIG. 3.—**Effect of Blood Pressure on Salivary Secretion.**

The first drop in the upper curve is the result of an injection of pilocarpine. The saliva shown, drop by drop, in the upper of the two signal lines, flowed rapidly when the blood pressure had risen. At *a*, blood was removed. At *b* and *c*, defibrinated blood was reinjected. At *d*, 6 per cent. gum-saline injected. At *e*, blood was removed. Time—10″ intervals.

the coronary arteries was below about 90 mm. of mercury, the heart began to suffer in efficiency. Dolley has shown (1909, 1910) that marked changes

in nerve cells ensue from hæmorrhage. In cats, recent experiments have shown me that a blood pressure remaining at an average value of 58 mm. for one hour stopped the appearance of vaso-motor reflexes and reduced the rate of respiration to about 6 or less per minute (see Fig. 4). An injection of gum-saline at this point restored the vaso-motor reflexes, but although artificial respiration was carried on for an hour, the normal respiration did not return, and when the artificial respiration was stopped, the animal died of asphyxia (see Fig. 34 below, which is a continuation of Fig. 4). Various other experiments showed that one and a half to two hours' exposure to a blood pressure from 70 mm. downwards resulted in paralysis of the bulbar centres in the cat. If the anæmia has not lasted too long, recovery may be obtained, as the experiments of Stewart, Guthrie, Burns, and Pike (1906) show. It is interesting to note that the different centres in the bulb vary in their resistance. In the cat, the respiratory centre suffers before the vaso-motor centre, although it may continue to discharge at the low and ineffective rate of 3 or 4 per minute, when the vaso-motor centre has lost its excitability. But, as the experiment quoted above shows, it cannot be recovered as readily as the latter centre can. It seems probable that different animals behave differently as regards the order in which their centres fail. The phenomena of shock in man suggest that the vaso-motor centre may begin to lose its excitability early.

It is extremely likely that a fall of blood pressure not great enough, or of insufficient duration, to

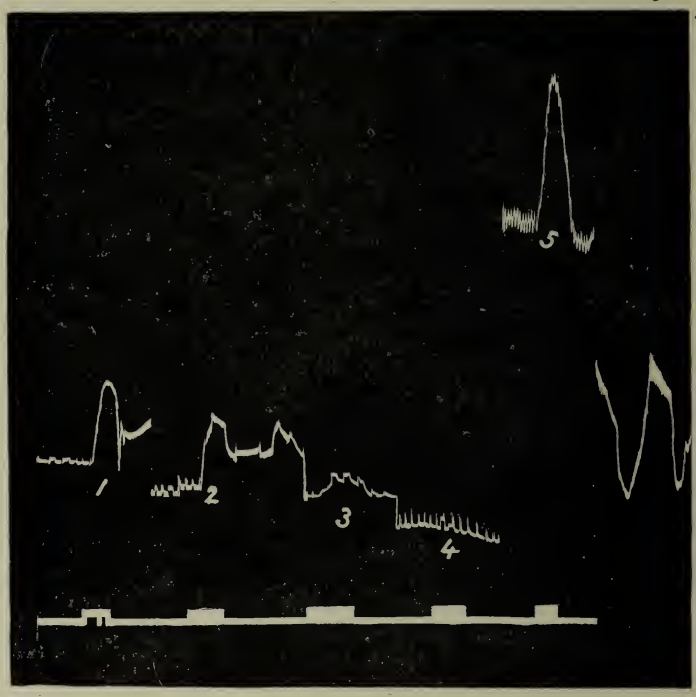

FIG. 4.—**Paralysis of Vaso-Motor and Respiratory Centres by Low Blood Pressure.**

Upper curve—blood pressure, lowered by previous hæmorrhage.

The central end of the sciatic nerve was stimulated with equal strength of induction shocks at the points signalled on the bottom line, the fourth stimulation being ineffective at about one hour after removal of 43 per cent. of the blood.

The respirations had, before this, fallen to six per minute. Before the fifth stimulation, the blood lost had been replaced by gum-saline. The norma rate of respiration did not return, so that artificial respiration was given. The excitability of the vaso-motor centre returned with the rise of blood pressure, but that of the respiratory centre did not. The last part of the curve shows the result of stopping the artificial respiration, the waves being due to the deep slow gasps at about three per minute, insufficient to prevent death from asphyxia. (See also Fig. 34 below.)

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[1] The percentages of blood removed, as given in this volume, are based on a blood volume equal to $\frac{1}{20}$ of the body weight. Observations by the "vital red" method indicate $\frac{1}{13}$ as more correct. To convert the numbers, as given, to this standard, multiply by $\frac{13}{20}$.

paralyse nerve centres will leave behind effects that may take long to disappear. The same may be said of prolonged defect of oxygen supply in other ways, as after exposure to pulmonary irritant gases, such as chlorine or phosgene. Investigations from this point of view are, I believe, in progress, and will lead to valuable information on the delayed effects of low blood pressure and of asphyxial conditions.

An unfortunate circumstance meets us here. If the paralysis of the vaso-motor centre has lasted so long as to be beyond recovery, no kind of transfusion is of any avail as a remedial agent in wound shock. In an animal with the spinal cord cut in the cervical region, the blood vessels are deprived of the control of the bulbar vaso-motor centre. The low blood pressure in this state cannot, according to my experience, be raised for more than a few minutes by intravenous injection of any kind. Each injection causes a temporary rise, soon followed by a fall to the original level (Fig. 58). I have been unable to discover why this is so. The venous pressure rises scarcely at all, until a very large volume of fluid has been introduced, so that the failure cannot be ascribed to weakness or obstruction of the cardiac contractions (Bayliss, 1916).

Cannon (communication to the Shock Committee) finds that, by introduction of fluid into the pericardium, the arterial pressure may be kept at 60 mm. of mercury for an hour, and on release of the pericardial pressure, then returns to normal. If repeated for another hour, the return is incomplete, and, after a third hour, does not recover at all.

Bainbridge suggests that the rise of venous pressure in such a procedure may entail loss of fluid from the capillaries and failure to return to normal owing to decreased blood volume. It seems that the possibility might be tested by injections of gum, which should restore the pressure if the vaso-motor centre is intact.

Gas Gangrene.—Many writers have stated that a good circulation of blood is one of the most potent factors in preventing the spread of this infection. The fact is not surprising in view of the anaerobic nature of the process.

2. Slight Hæmorrhage in Combination with other Factors.

Wound shock is probably, in most cases, due to a combination of several factors, each in itself not necessarily serious. The part played by each of these naturally varies in individual cases. Some of those mentioned below are experimental only, most of them both experimental and obtained by observation of wounded men. It will be noted that practically all of them are exaggerated by a small degree of hæmorrhage.

A. **Injury to Muscles.**—Cowell (1917, pp. 15 and 65) remarks that multiple wounds are very likely to cause a marked fall in blood pressure, although the hæmorrhage may only have been slight. In experiments with Major Cannon, we found that injury to the thigh muscles in the cat leads to a fall of blood pressure, and I have recently noticed that this fall is greatly increased by a small loss of blood, such as would have had no injurious

effect in a normal cat, and been quickly recovered from. This question will be discussed further below.

B. **Exposure to Cold.**—There is a general agreement that the effects of cold on wounded men are very injurious. One of the most important ways of reducing shock is keeping the patient warm during transit to the Casualty Clearing Station.

In the course of experiments on the effects of cooling on cats, Cannon and I found that their rectal temperature could be reduced to 25° C. by the application of ice, and that complete recovery took place on warming, unless the application of cold had been accompanied by loss of blood, even comparatively small. In this latter case, treatment is necessary. The fall of temperature is accompanied by a fall in blood pressure, which appears to have its main cause in slowing of the heart beat; at all events, the two phenomena run a parallel course (see Figs. 35, 36, and 37).

C. **Deficiency of Oxygen Owing to Asphyxia.**—Breathing air deficient in oxygen for half an hour was found by Cannon and myself to have permanent bad effects on cats. These effects were decidedly worse after slight hæmorrhage (see Figs. 26, 49, and 50).

D. **Anæsthetics.**—Ether, given for operations, is frequently found to increase the state of shock. In experimental work it is a difficult matter to maintain ether anæsthesia in the cat without some degree of deficiency of oxygen in the blood, as indicated by its dark colour. The effects of certain anæsthetics are probably another aspect of the facts of the preceding paragraph.

E. **Injection of Acid.**—Sometimes the injection of acid into a vein leads to progressive fall of blood pressure. When this occurs, it is intensified by slight hæmorrhage, and when acid has not produced a fall of pressure, this can usually be brought about by removing a small amount of blood, such as would have no effect on a normal cat (see Figs. 21, 22, 23, and 55).

F. **Temporary Occlusion of the Aorta.**—"Shock" is often obtained on readmission of blood after obstruction of the aorta for an hour or so. A slight hæmorrhage increases the effect in this case also (see Figs. 52, 53, and 54).

These facts will be sufficient for the present to prove the importance of keeping up a satisfactory supply of blood to the various parts of the body.

In experiments in the laboratory, one finds that **as the blood pressure is raised the various other symptoms associated with shock disappear.** One of the most striking of these is the rapid, shallow respiration. Injection of gum solution almost at once reduces it to the normal rate and depth (see Figs. 5 and 14).

It may have been noticed that one of the above headings included the vexed question of the part played by "acidosis" in shock. This problem will be discussed in more detail in connection with the use of alkaline solutions.

THE MEASUREMENT OF THE ARTERIAL PRESSURE

This being, as we have seen, so important a matter, it is worth while to refer to the very con-

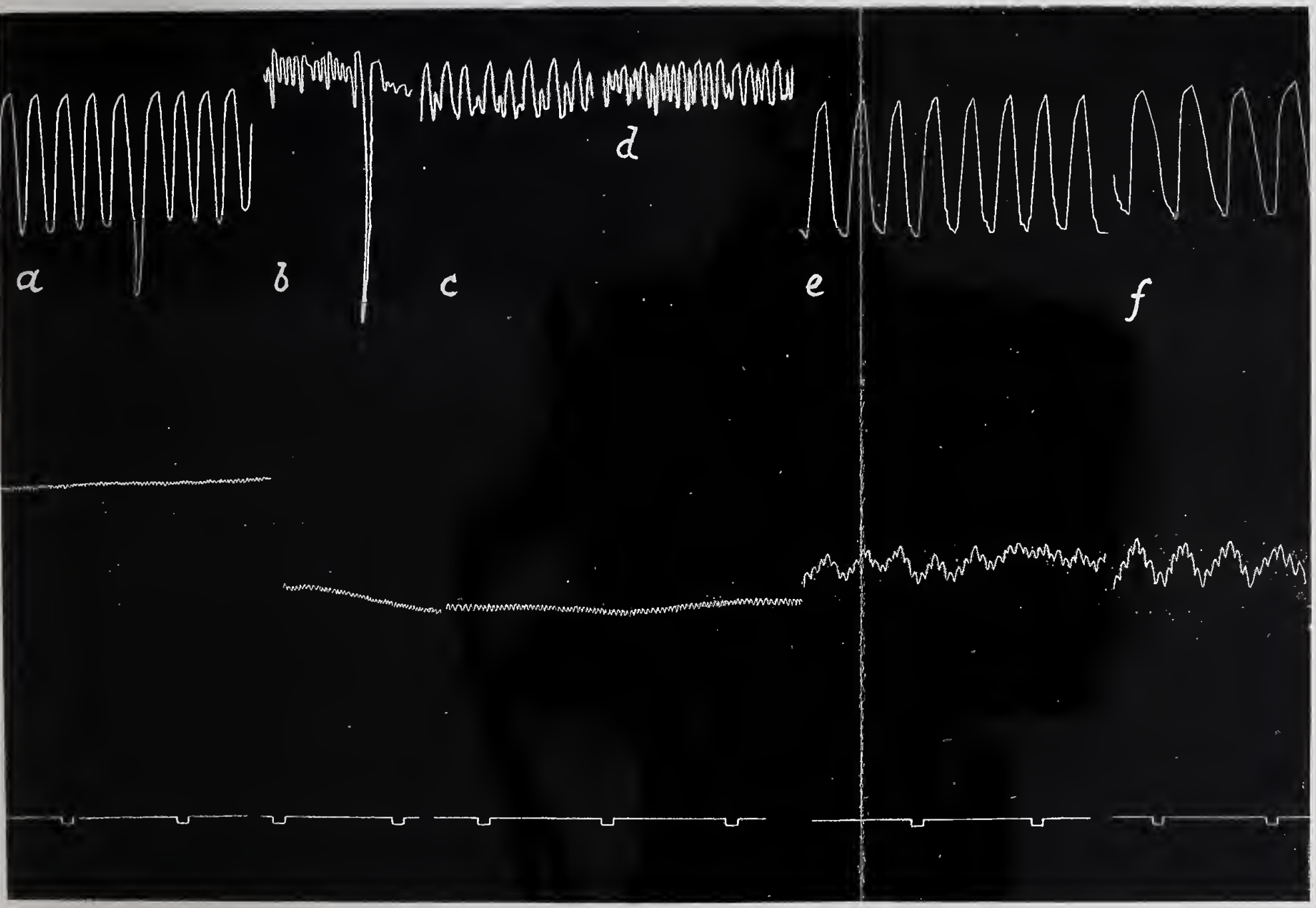


FIG. 5.—**"Shock" Type of Respiration after Muscle Injury Cured by Gum.**

Spinal cord cut in upper lumbar region.
Upper tracing—respiration by insertion of lever between liver and diaphragm.
Lower tracing—blood pressure.
Time signal—10″.
a, Normal. *b*, Immediately after injury. *c*, Somewhat later. The rate has decreased. *d*, After massage of legs. *e*, After injection of gum-saline. *f*, Two hours later. Blood pressure zero—bottom of figure.

[*To face page* 16.

venient modification of the Riva-Rocci apparatus, known as the "Tycos" sphygmomanometer (Fig. 6). This instrument is made by Messrs Short & Mason, 46A Holborn Viaduct. It is easily and rapidly applied. The manometer, being of the metallic gauge type, is easy to read, although for extreme accuracy, calibration against a mercury

FIG. 6.—"Tycos" Sphygmomanometer. Method of Auscultation. (By the kindness of Messrs Short & Mason.)

manometer may be required at intervals. But this is unnecessary for clinical purposes. It is probably better to use the auscultatory method for estimation of the systolic and diastolic pressures, but it appears that more reliance is to be placed on the former. The interpretation of the Korotkov sounds at the diastolic level is, as yet, somewhat uncertain. The difference between the two pressures, the "pulse pressure," is an index of the heart output, amongst

other things, and is valuable as a clinical method. Bazett (1918) has made a large number of measurements of this kind, and been able to deduce certain laws. Oliver (1916, p. 9) describes a useful "phonendoscope" for the auditory method. It is to be obtained from Hawksley, 357 Oxford St.

RAISING THE ARTERIAL PRESSURE

The improvement of the blood supply by raising the arterial pressure being one of the most important means of treatment of wound shock, we have next to inquire how this is best done.

There are two ways in which the arterial pressure may be raised. We may use **drugs which constrict arterioles**. The peripheral resistance being thus increased, the same force of heart beat as before produces a higher pressure. On the other hand, we may raise the pressure by increasing the volume of blood in circulation, without altering the peripheral resistance. This is done by introducing into a vein an appropriate liquid.

As already pointed out, the end to be attained is not the height of the blood pressure in itself, but a better supply of blood to the tissues. This being so, it will be obvious that the former method is a bad one, since, although the driving pressure in the main arteries rises, the effect on the supply to an organ is more or less counteracted by the constriction of the arterioles in that organ. It is therefore unnecessary to spend much time in consideration of the use of vaso-constrictor drugs. I will only refer briefly to three that have been used for the purpose of raising the blood pressure.

Adrenaline.—From the work of Elliott (1912), and Cannon (1911), it is practically certain that adrenaline is present in the blood of wounded men, and Bedford (1917) has shown that this is the case in experimental shock. Moreover, the effect of an injection is very brief. Bainbridge and Trevan (1917) have shown that repeated large doses result, experimentally, in a shock-like condition.

Pituitrin is better, since the effect is more permanent.

Barium Chloride.—This was used by Langley (1912) to raise the blood pressure in cats after decerebration by injection of starch into the carotid artery. I found it effective in doses of one milligram per kilo of body weight and innocuous. At one time I suggested that it might be of use in wound shock, but further investigation has convinced me that such use is wrong in principle, and I would deprecate the use of any vaso-constrictor drug.

As mentioned above, the observation of surgeons has failed to find any evidence of accumulation of blood in the abdominal area, whether in artery or vein, in wound shock. So that there is no object to be attained by causing these vessels to contract.

What we have to do is to make use of the other method, the really effective one, by which a better supply to the organs, especially to the brain and heart, is ensured. By **intravenous injection** of an appropriate fluid in sufficient quantity the blood pressure is raised, while the channels through which the blood is supplied to the organs are not obstructed. Hence these organs receive the full benefit of the increased driving pressure. The function of the

extra volume of fluid introduced is not only to replace that lost to the exterior by obvious hæmorrhage, but also that lost to currency by stagnation in certain regions, probably capillary areas. In the latter case, the function of the injection may be said to be more or less temporary only, being to keep vital organs in sufficient activity until the state of stasis, associated with shock, has been recovered from.

THE FLUID TO BE USED

Blood.—The next problem is, what fluid is to be used for the purpose?

It seems obvious that blood itself is the most appropriate fluid to replace blood, and there is no doubt as to its efficacy. On the other hand, to my surprise, it has not shown itself, experimentally, to be so much superior to certain artificial solutions, such as gum arabic, as I expected. In the experiments to which I refer it was found that, if gum was useless, so also was blood. But it is very probable that there is a stage in the progress of shock at which blood is more effective than gum. I am at present trying to find out this stage, but as far as the experiments hitherto performed indicate, it seems to be a brief one. It would appear that the degree of dilution of the blood by the amount of gum solution put in does not reduce the hæmoglobin value to any serious extent.

In normal blood there is evidently a notable reserve of hæmoglobin, in relation to the requirements of the body at rest. It may thus be diluted to some degree without becoming deficient, as long

as rest is maintained. Captain Bazett has noticed a reduction of the hæmoglobin to as little as 35 per cent. of the normal value, the patients nevertheless doing well. He regards 25 per cent. as the lowest limit, if recovery is to take place. Rous and Wilson (1918) state that rabbits may have three-quarters to four-fifths of their hæmoglobin removed, although they show a certain degree of dyspnœa on exertion. These authors conclude that it is rarely, if ever, necessary to supply blood corpuscles after casualties in the field. Cannon has removed as much as 75 per cent. of the blood from cats, and replaced it with gum solution without harm.

On the other hand, experience at some Casualty Clearing Stations indicates that there are cases in which blood may be effective, while gum is not so. Some of these cases may be discounted, on account of the custom in some places not to expend the more valuable resources in blood on what were regarded as hopeless cases, gum being given to these. But it seems very probable that there may be a stage in the progressive effects of low blood pressure on the nerve centres in which blood restores, while a solution devoid of hæmoglobin may not do so. I have at present experiments in progress to test this. So far as these experiments have gone, they indicate that the margin is a very narrow one.

Although the value of transfusion of blood is undoubted, there are some disadvantages which cannot be overlooked. Drummond and Taylor (1918) refer to the difficulty of obtaining sufficient donors for direct transfusion under some circumstances. Tests of compatibility are necessary,

although the method is now simple (see Robertson, 1918). If preserved blood or corpuscles be used, it is clear that difficulties of always keeping a stock ready for use arise, while the quantity required after a battle may be great. Under press of time and limited staff, the use of an artificial solution is easier and quicker.

The reader is referred to the memorandum by Captain Oswald Robertson (1918) for details as to the various methods of transfusion and of preservation of blood.

Blood is the ideal fluid beyond question, but there can be no doubt that the discovery of an efficient substitute, even if not quite so perfect as blood, is a matter of some importance.

The various solutions proposed may next occupy our attention.

ARTIFICIAL SOLUTIONS FOR INTRAVENOUS USE

Ringer's Solution.—It was natural that simple isotonic salt solutions should be tried, on account of their routine use in the laboratory for the perfusion of the heart and isolated organs. It was, however, soon found that such solutions were useless in restoring a low blood pressure in wounded men. There is general agreement on this point. Fraser and Cowell (1917, p. 16) say: "We have been greatly disappointed with the results obtained, and blood pressure readings confirm the clinical disappointments which we have experienced." It has been found that the temporary rise is rapidly followed by a fall, which

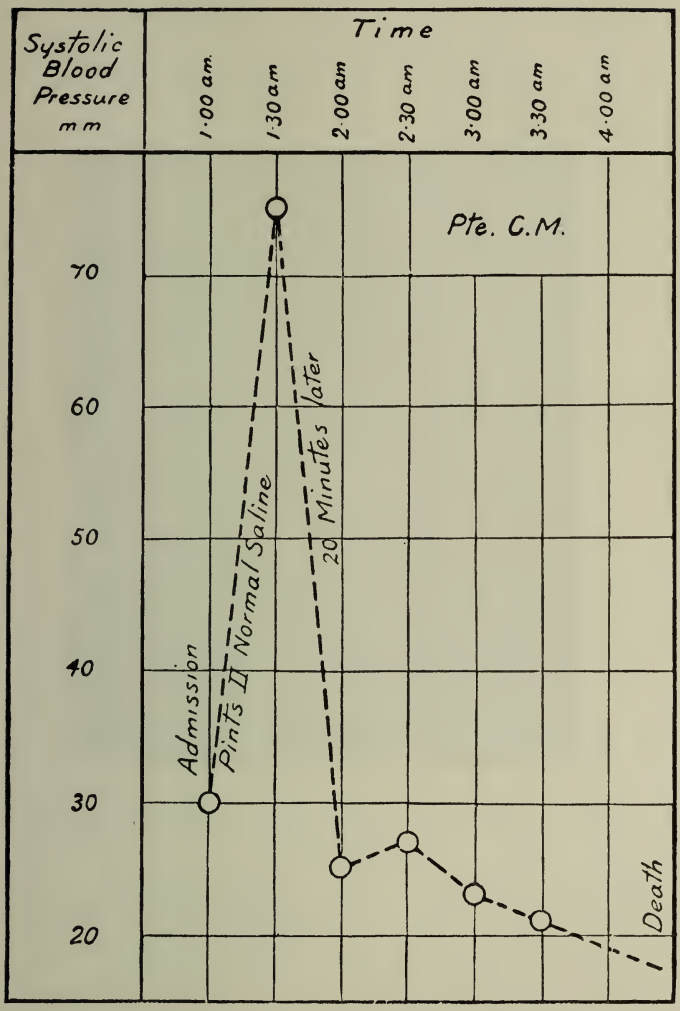


FIG. 7.—**Effect of Isotonic Saline in Low Blood Pressure.**

Severe shell wound. Collapsed and pulseless. Two pints of normal saline solution given intravenously. Pressure rose to 75 mm. of mercury, but began to fall rapidly in twenty minutes, and within an hour was lower than before the infusion. Death occurred some three hours later. (Fraser and Cowell, 1917, p. 16.)

may even proceed to a lower level than before the injection. The case given in Fig. 7 is stated to be "typical of many which we have recorded."

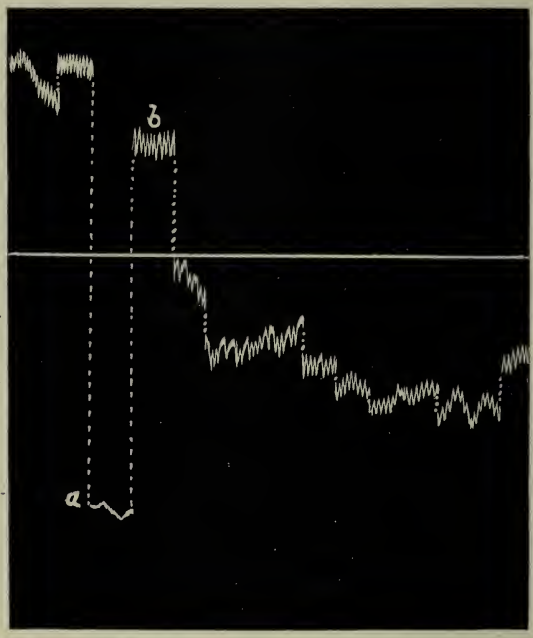


FIG. 8.—**Failure of Ringer's Solution to Restore Blood Pressure in Cats.**

The horizontal line is at the level of 100 mm. of mercury.

32 per cent. of the blood was removed, reducing the blood pressure to the level at *a*. An equal volume of warmed Ringer's solution raised it to *b*. Each succeeding step in the tracing is at ten minutes interval. After twenty minutes the respiration became slow, periodic, and with deep inspiratory gasps.

Experiments on cats confirm this experience, and enable a further analysis of the cause to be made. If a part of the blood be removed and immediately replaced by an equal volume of Ringer's solution,

the blood pressure is not completely restored to its original height, and, within half an hour or so, it returns to the low level or below it (Fig. 8).

Sherrington and Copeman (1893) showed, by measurements of the specific gravity of the blood, that salt solutions leave the circulation in less than half an hour.

	Viscosity.		Osmotic Pressure.	
	$H_2O = 1$.	Dynes $\times 10^3$ ($H_2O = 6{\cdot}6$).	Against H_2O mm. Hg.	Against Ringer's solution mm. Hg.
Blood of cat	3·0	19·8	...	...
Ox serum	1·5	9·9	116	36-40
Soluble starch (Kahlbaum), 4 per cent.	1·7	11·2	...	14-16
Soluble starch, 4 per cent. after cold storage	2·26	16·0	...	...
Wheat starch, 2 per cent.	2·65	17·5	...	...
Amylopectin, 1·72 per cent.	4·8	32	...	...
Gum acacia, Ca salt, 7 per cent.	3·1	20·5	...	...
Gum acacia, Na salt, 7 per cent.	3·4	22·5	218	39
Gelatin, 6 per cent.	4·0	26·4	95	38·5
Gelatin, 6 per cent., after heating to 100°	3·0	19·8	...	63
Dextrin, 4 per cent.	1·17	7·7	...	36

The explanation of the fact that an equal volume of salt solution does not raise the blood pressure to its normal value is easily explained by the want of viscosity. Since the peripheral resistance in the blood vessels is due to the internal friction of the

liquid passing through, it is clear that any decrease in this viscosity, such as would be produced by dilution of the blood with a liquid of lower viscosity, results in a fall in peripheral resistance and, consequently, in arterial pressure. Ringer's solution has a viscosity practically the same as that of water, while that of blood is three or more times that of water. The table on p. 25 gives a few values of viscosities and osmotic pressures of solutions which are of interest in the problem before us.

The reason why saline solutions leave the circulation rapidly is equally clear, but requires a rather longer discussion. It is, however, of fundamental importance. Starling's work on lymph production (1896) gives us the clue. There are two facts to be remembered at the outset. In the first place, there are colloids, chiefly proteins, in the blood, and these are such as to have an osmotic pressure of between 30 and 40 mm. of mercury. This means that, if separated from water or Ringer's solution by a membrane impermeable to colloids, permeable to salts, water will be attracted with a certain force. Now, in the second place, the wall of the blood vessels is normally such a membrane, as shown by Scott (1916). But the blood pressure in the small arteries and beginning of the capillary area is higher than the osmotic pressure of the blood colloids, so that their tendency to attract water is overpowered and a liquid (lymph) is pressed out by filtration. This liquid has the composition of blood minus its colloidal constituents (including, of course, the corpuscles) and it passes into the tissue spaces. The reader will remember that there is every reason to

believe that a similar process takes place in the glomeruli of the kidney, being the first stage in the separation of urine.

As we follow the blood in its course along the capillaries we soon arrive at a region where the filtration pressure of the blood is equal to the osmotic pressure of the colloids, and then to one where this blood pressure is lower than the osmotic pressure. In this latter region the osmotic pressure of the blood colloids gains the upper hand and reabsorbs the lymph formed in the more arterial area. But this process of reabsorption is not always adequate to remove the whole of the lymph filtered out, and the remainder is carried away by the lymphatic channels, to be returned to the blood via the thoracic duct.

Next suppose that the blood has been diluted by the admixture of a solution containing no colloids, or only such as have no osmotic pressure—starch, for example. The effect of this will be shown in several ways. The colloidal osmotic pressure of the blood being reduced, the pressure available for filtration (that is, the difference between the blood pressure and the colloidal osmotic pressure) is increased, and filtration in the arterial areas is accelerated. Moreover, we must proceed further along the stream before we arrive at the place where the blood pressure is lower than the lowered colloidal osmotic pressure, so that the area in which filtration takes place is increased, while at the same time that of reabsorption is reduced. The force causing reabsorption (the colloidal osmotic pressure) is also lowered by dilution of the blood. The net

result of the combination of these factors is a disappearance of liquid from the blood. The lymphatics being unable to remove it sufficiently rapidly, œdema of the tissues is brought about.

It is a common experience, in fact, that perfusion of organs with saline solutions soon leads to œdema. The experiments of Knowlton and Starling (1912) with the heart-lung preparation indicate that œdema of the lungs is apt to be produced, especially in cats. The blood used in this work was always more or less diluted with Ringer's solution.

It is easy to follow the disappearance of the injected liquid from the blood by taking hæmoglobin estimations or hæmatocrite measurements at intervals after the injection. These show that the hæmoglobin percentage soon begins to rise again after the introduction of a saline solution. In the case of Fig. 8, the blood two and a half hours after the injection had a volume of corpuscles equal to 28 per cent. of the blood, the normal value in the cat being about 33 per cent. The first dilution by the liquid introduced would have reduced the value to 22 per cent.

The final result of injecting saline solutions, as remarked above, is usually a fall in blood pressure below the value at the moment of injection. This is probably due to the progressive effect of the deficient supply of blood to the brain and other tissues.

Hypertonic Saline.

Solutions containing 2 per cent. of sodium chloride have been frequently recommended and used, doubtless with the idea of attracting water to

the blood by means of the osmotic pressure of the salt, or at any rate of preventing its loss. We must consider the evidence, both theoretical and practical, in relation to the efficacy of this procedure.

The use of such solutions has had success in cholera, but the conditions are different in this disease, since large quantities of water are lost from the intestine and the blood becomes very thick. Probably a hypertonic solution may also retard the loss from the intestine.

Whether the blood may become concentrated by loss of liquid in the late stages of severe wound shock is a disputed question. But there is no evidence that it occurs at the time when most cases have to be treated. According to Cannon, Fraser, and Hooper (1917), there is an increase in the concentration of corpuscles in the capillary blood as compared with the venous blood. The effect of low blood pressure in itself is well known to be a dilution of the blood by absorbing liquid from the tissues. It may be explained by the considerations of the preceding section, since the filtration pressure being decreased, the osmotic pressure of the colloids has the greater preponderance in absorbing water.

According to Cannon (1918), thirst is due to dryness of the throat on account of defective secretion of saliva. If the blood becomes more concentrated, as after sweating, the osmotic mechanism of the secretory cells, by which water is passed from the blood to the ducts, works under greater difficulties, because more work is required to remove water from a concentrated solution than from a dilute solution. The addition of salts to the blood

by injection of hypertonic solutions would have this effect also; so that thirst would result, just as it does from taking excess of salt by the stomach.

In cats, the temporary rise of blood pressure

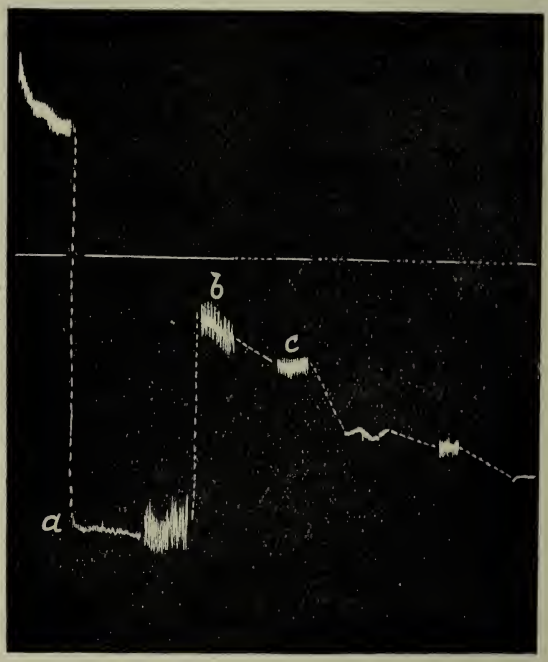


FIG. 9.—Effect of Hypertonic Saline in the Cat.

Under urethane, 60 per cent. of the blood removed in stages until the blood pressure reached the level at *a*.

b. A quarter of an hour after injection of an equal volume of 2 per cent. sodium chloride. The first effect of the injection was to slow the heart and to produce gasping respirations.

c. Half an hour after injection.

Each later level at half-hour intervals, so that the last was at two hours after the injection.

Horizontal line at 100 mm. of mercury.

This curve should be compared with that of Fig. 29 (p. 82) in which 5 per cent. gum in Ringer's solution was given in an experiment made otherwise in precisely the same way as the above, except that rather more blood (66 per cent.) was removed.

produced by hypertonic saline lasts very little longer than that from Ringer's solution (see Fig. 9).

Fraser and Cowell (1917, p. 18) report a case of collapse after operation for severe shell wound of the pelvis, which, although ultimate recovery took place, indicates a rapid loss of the solution injected. The blood pressure was, on admission, 90 mm. It fell to 25 mm. after operation and was raised to 100 mm. by the injection of two pints of hypertonic saline. But it fell again in an hour to 65 mm. A spontaneous slow recovery took place subsequently.

Drummond and Taylor (1918, p. 1) remark: "Formerly we made use of intravenous injections of normal or hypertonic salt solutions, but these were abandoned, as the rise of blood pressure and benefit to the patient were so transitory."

It appears to me that the reason for these failures is not far to seek. The raised osmotic pressure of the salts in the blood attracts, for a short time, water from the tissues; but, since the blood vessels are freely permeable to salts, an equalisation of salt concentration within and without soon takes place, so that there is no longer any osmotic force arising from this source. At the same time, the colloid concentration has been reduced both by the solution injected and by the liquid absorbed from the tissues. Hence the conditions for rapid filtration are now much the same as after the injection of isotonic salt solution.

Hypertonic saline solutions lead to œdema when perfused through the kidney, and the loss of fluid from the blood after intravenous injection of such solutions can readily be followed by hæmoglobin

determinations. Hypertonic solutions require careful injection. I have occasionally seen unpleasant symptoms, gasping respiration and slowing of the heart. On the whole it does not seem to be desirable to add to the saline content of the organism.

Cannon, Fraser, and Hooper (1917, p. 37) mention a rather curious effect of hypertonic salt solution. A case of compound fracture of the tibia and fibula, with hæmorrhage, gave on admission a blood corpuscle count of 4,200,000 in the venous blood, with 94 per cent. of the normal hæmoglobin content. Six hours after injection of two pints of 2 per cent. saline, the capillary count was 4,120,000, practically the same as the previous venous count, but the hæmoglobin was only 55 per cent. of the normal. This shows a loss of hæmoglobin from the corpuscles, and the authors remark on this as a serious disturbance.

We may conclude that hypertonic salt solutions are very little better than isotonic solutions and may sometimes be dangerous.

The addition of **Calcium** in amounts in excess of the normal content of Ringer's solution has been recommended on two grounds :—

1. **Vaso-constrictor** Action. This is no real advantage, as we saw above. Moreover, it is very transitory (Fig. 10).

To raise the blood pressure to an equal extent by the injection of an appropriate non-constrictor solution (such as gum arabic) ensures an increased blood supply to the organs, while the corresponding rise by arterial constriction has not this effect. It is true that the work of the heart is increased some-

what in the former case, because the output per unit time is raised. But, as already pointed out, there are no signs that the contractile power of the heart has suffered in shock. The fact that it can maintain a high blood pressure after blood transfusion or gum injection shows that the cardiac contractions are normal in strength.

If vaso-constriction is desired, as may possibly be the case when vascular dilatation is known to be present in a wide area, a **barium** salt is far more effective than a calcium one. Barium chloride was used by Langley (1912) for the purpose of raising the blood pressure in decerebrate cats. I found also one milligram of barium chloride per kilo body weight to be innocuous to cats and to have a prolonged vaso-constrictor effect. A slight stiffness in movement was noticed on the day of injection, but it had disappeared the next day. I feel very doubtful, however, whether anything is really gained by its use. Take the experimental case of the spinal cat, where it is presumed that the excitability of the spinal cord is depressed by the low blood supply. If we give barium chloride, we certainly raise the blood pressure, but we constrict the arterioles in the cord at the same time. Hence its blood supply is probably really decreased, notwithstanding the

FIG. 10.—Effect of Calcium Chloride.

Injection of 5 c.c. of 1·1 per cent. calcium chloride at *a*. Effect lasted about thirteen minutes.

raised arterial pressure. Even a small narrowing of the arterioles has a powerful effect in diminishing the blood flow through the capillaries.

2. Calcium has been supposed to decrease the **permeability** of the blood vessels, because of its known effect in bringing about the coagulation of colloids. If this were so, escape of fluid from the vessels might be prevented, with the absence of œdema and transudations in general.

To test this, I compared the rate of escape from the blood of ordinary Ringer's solution with that of a similar solution to which excess of calcium chloride had been added. I was unable to detect any difference. Boycott (1918) finds that the lung œdema of goats gassed by chloropicrin or phosgene is not decreased by subcutaneous injection of 1 per cent. calcium chloride in doses of 10 c.c. per kilo.

Chiari and Januschke (1910) state that the blistering effect of oil of mustard is prevented by previous hypodermic injection of calcium chloride. Cushny has tested this result in connection with the action of the so-called "mustard gas" (di-chlorethyl-sulphide) and was unable to confirm the statement.

If the addition of more than the normal amount of calcium to the blood is of benefit, subsequent removal of the excess by means of sodium citrate should deprive the animal of this benefit. Tested experimentally, no effect of any kind was produced by the injection of the required amount of sodium citrate.

There is no evidence, then, that the addition of calcium salts to a solution for intravenous injection has any beneficial effect whatever.

Alkaline (Bicarbonate) Injections.

The recommendation to make use of alkaline solutions assumes that "acidosis" is a potent factor in the phenomena of wound shock. After careful examination of the evidence, I have been compelled to come to the conclusion that the importance of the state has been greatly exaggerated, not only in wound shock but in general. The use of bicarbonate solutions is unnecessary, their effect being better attained by merely raising the blood pressure.

Since the question is a much disputed one, a somewhat detailed discussion is advisable.

In the first place, as a salt merely, a 4 per cent. solution of sodium bicarbonate, the concentration recommended, has the same effect as a hypertonic solution of sodium chloride, with the same advantage or disadvantage. But it is not used for this purpose, but to combat "acidosis."

What then do we mean by this statement?

Normal blood contains a certain percentage of sodium bicarbonate and, as Lawrence Henderson (1913, pp. 140-163) has so well shown, can never become more than just faintly more acid than distilled water so long as there is any bicarbonate left in it.

But the normal bicarbonate content of the blood may be reduced, owing to reaction with non-volatile acids produced in the tissues (lactic, hydroxybutyric, etc.). When more than a small amount of the bicarbonate has been replaced by the sodium salts of such acids, or when the plasma gives off less than the normal 55 volumes of carbon dioxide when acted on by sulphuric acid in a vacuum, after

exposure to air containing 5·5 per cent. CO_2, it has been suggested by Van Slyke and Cullen (1917) that the state should be regarded as one of "acidosis." I venture to think this unfortunate, because it suggests that there is a real increase in acidity, or, to put it more correctly, in hydrogen-ion concentration. As we shall see presently, this is not necessarily the case. To obviate the objection somewhat, Van Slyke introduces the terms "compensated" and "uncompensated acidosis." But the latter is the only true "acidosis."

No one supposes that the presence of a small amount of sodium lactate in the blood is of any consequence at all; it is soon removed by oxidation, forming bicarbonate again. But does the decrease in the bicarbonate matter? In itself, we may say definitely that it does not. Bohr (1891) and Buckmaster (1917, 1918) have shown that it cannot act as a *carrier of* carbon dioxide, since it loses none at the tension of carbon dioxide in the alveoli of the lungs. The tension in fact in this situation is 42 mm. of mercury, whereas the tension at which carbon dioxide begins to be given off from a solution of bicarbonate at 38° C. is 3-4 mm. of mercury (Buckmaster). All the alkali present in the blood must always be in the state of bicarbonate, both in arteries and veins, a fact indeed which is the basis of Van Slyke's method of determining the "alkaline reserve" of the blood. It is never decomposed, except by the addition of a stronger acid.

Cannon (1917, p. 78), however, has suggested that decrease of bicarbonate may play a part in reducing the rate at which acid products formed

in the tissues diffuse into the blood and become neutralised, or, conversely, the rate at which bicarbonate itself passes into the tissue cells for the purpose of neutralising acid produced therein. This is probably the case, but it does not imply that the appropriate treatment is to inject bicarbonate solution into the blood. The cause of the reduced bicarbonate in the blood is the production of fixed acids on account of deficient blood supply and consequent incomplete oxidative reactions. It would be more rational to remove the cause by raising the blood pressure, rather than to attempt to neutralise the results without preventing their continued formation.

But, as Cannon (1917, p. 41) has shown, there is usually a defective alkaline reserve in wound shock, so that it is of importance to examine more closely what this may involve and what it implies.

When we proceed to consider the numerous effects said to be due to acidosis, we find that they are all, with the exception of that one above mentioned, hydrogen-ion effects. In other words, they are caused by production of acid reaction in the blood. "Acidosis" is regarded by Van Slyke as serious when the bicarbonate reserve is reduced to less than five-sixths of its normal value. Does such a change result in a sufficient increase in the hydrogen-ion concentration to be of any importance? And what is the increase that has been found to give rise to the various effects referred to?

A bicarbonate solution always contains some dissolved carbon dioxide from hydrolysis of the salt, and Lawrence Henderson (1908) has shown how

the hydrogen-ion concentration is expressed by the ratio of the carbonic acid to the sodium bicarbonate present. To put the matter simply, but less correctly, the acidity of the blood is due to the carbon dioxide, the alkalinity to the bicarbonate. When the latter decreases, while the former increases or remains constant, the hydrogen-ion goes up. If the carbon dioxide decreases while the bicarbonate remains constant, the hydrogen-ion goes down. To maintain the hydrogen-ion constant, both the carbon dioxide and the bicarbonate must increase or decrease in relative proportion.

We have seen that when fixed acid is formed in the tissues, carbon dioxide is driven off from a part of the bicarbonate. Thus, for a time, there is an increase in the hydrogen-ion of the blood, both by increase of carbon dioxide and by decrease of bicarbonate. But what will happen when this blood arrives at the respiratory centre? The increased hydrogen-ion concentration excites the centre to increased activity, the ventilation of the lungs increases and carbon dioxide is removed until the centre ceases to be stimulated, that is, until the hydrogen-ion concentration has been reduced to normal by removal of carbon dioxide in sufficient amount to reduce the ratio $H_2CO_3/NaHCO_3$ to its normal value.

In order to test this deduction by experiment, cats were anæsthetised with urethane, ether or chloralose, and given intravenous injections of half-normal hydrochloric acid in amount sufficient to reduce the bicarbonate reserve by one-third, as found in previous experiments by Cannon and myself, in

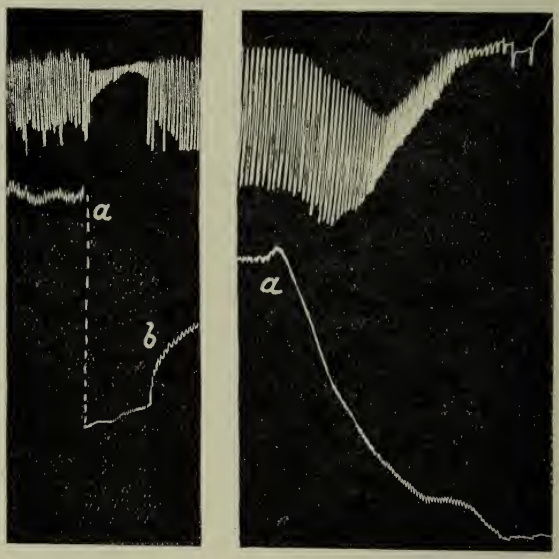
which the bicarbonate concentrations were determined by Van Slyke's method. The hydrogen-ion concentration of the blood before and after the injection was compared by the use of neutral red. A sample of blood was drawn from the carotid artery into a centrifuge tube containing a small quantity of powdered oxalate, as for the Van Slyke determinations; this was immediately covered with liquid paraffin to a depth of one to two centimetres and centrifuged. A drop of 0·1 per cent. neutral red solution was added to the plasma by inserting a fine pipette through the paraffin, and the colour of the two samples compared. From the work of Sörensen (1909) it is obvious that neutral red is an appropriate indicator for the purpose, since it has a series of distinctive changes of tint from just above to just below the reaction of blood, which is close to the neutrality of water, and is but little affected by the presence of proteins and salts. Miss Homer (1917) has also tested its behaviour in plasma, and finds it more reliable than any other indicator. I have tried methyl red also, but its changes of tint are rather too far on the acid side.

In several experiments of the kind mentioned, made on healthy cats, there was no difference in tint to be detected between the samples before and after the injection of acid. In both cases, the colour was reddish-orange, corresponding to a hydrogen-ion concentration just on the alkaline side of neutrality.

This result, of course, is not really new. An experiment given by Van Slyke and Cullen (1917, p. 337) may be mentioned. They reduced the alkaline reserve to one-half by the injection of acid.

Dyspnœa resulted for ten minutes, and the hydrogen-ion concentration, which was originally expressed by the exponent 7·28, was found to be 7·23; the experimental error being 0·02, these are identical.

The same fact is brought out by Caldwell and Cleveland's (1917) observations on patients. They



A *B*

FIG. 11.—**Form of Respiration after Hæmorrhage.**

Upper tracings—respiration.
Lower tracings—blood pressure.

A. Rapid removal of blood at *a* caused quick, shallow respirations until the blood pressure rose again spontaneously at *b*.

B. At *a*, allowed to bleed to death by opening artery. Respiration at first quick and shallow, but, as paralysis of the centre progresses, the rate becomes slow, although still shallow.

noticed that there was no difference in the respiration when the bicarbonate figures were 50 or 43, nor in another case when they were 43 or 36, so

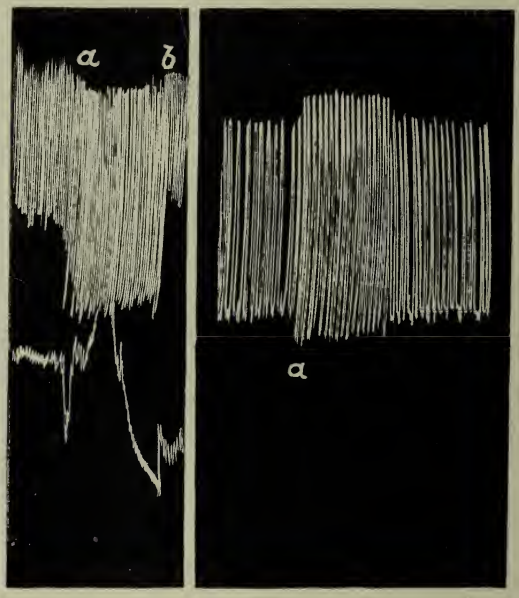
long as these were stationary values. There was hyperpnœa during the course of alteration from one to the other, clearly due to the removal of the excess carbon dioxide by the activity of the respiratory centre.

Haldane and Priestley (1905, p. 249) showed how extraordinarily sensitive the respiratory centre is to a slight increase of the hydrogen-ion concentration in the blood. A rise of the content in carbon dioxide of the inspired air to 2 per cent. increases the total ventilation of the lungs by 50 per cent., and the alveolar tension of carbon dioxide rises so little as to be undetectable. A rise in this latter tension from 40 to 41·6 mm. of mercury (that is, 0·2 per cent. of carbon dioxide) doubles ventilation.

It is of some importance to note that the form of respiration in shock is frequently described as rapid but *shallow*. This is similar to that produced experimentally in certain stages of hæmorrhage (Fig. 11) or by muscle injury (Fig. 5 above). It is quite different from that produced by increase of hydrogen-ion, which is also usually more rapid than normal, but at the same time deep (Fig. 12). It may be deeper without being quickened, especially in well-trained individuals. The former type does not result in more effective ventilation, whereas the latter does. The rapid shallow respiration of wound shock in itself does not indicate acidosis. What the meaning of it is, other than as an indication of low blood pressure, is at present uncertain and requires further investigation. Possibly, the *exaggerated Hering-Breuer reflex*, described by Haldane,

may play a part. That it is not due to acidosis is shown, experimentally, by the fact that it is relieved equally well by gum injections, with or without bicarbonate (Fig. 5).

A little more detail with respect to this important type of respiration may be of interest. The



A *B*

FIG. 12.—**Effect of Acid on Respiration.**

A. Carbon dioxide added to inspired air at *a*. *b*, Normal air again. The lower tracing shows the rise in blood pressure, followed by fall, lasting after the respiration has become normal again.

B. Lactic acid injected into vein at *a*.

reader will remember that, as the lungs are being stretched by the action of the inspiratory muscles, certain vagus nerve endings, or receptors, are stimulated. When this stimulation has reached a

particular degree of magnitude, the inspiration is inhibited, while expiration is excited. Normally, this inhibition does not occur until the lungs are distended to a large extent; but, under abnormal conditions, inhibition may occur very early in the course of inspiration, resulting in a shallow respiration. It naturally becomes rapid because the centre has only partially discharged in the previous respiratory effort and its excitability returns quickly. Moreover, owing to the ineffective nature of this shallow breathing, there is an abnormally high carbon dioxide content in the blood, which also excites the centre. It is clear that the premature inhibition might be produced in two ways. Either the vagus endings in the lungs are abnormally sensitive, as may be the case after exposure to pulmonary irritant gases, in the cases known as "disordered action of the heart" or the "effort syndrome," described by Haldane, Meakins, and Priestley (1918); or, the respiratory centre may be abnormally sensitive to the normal degree of stimulation of the vagus receptors. This latter explanation seems the more probable one in the cases where the type of respiration comes on after wound shock or hæmorrhage. Fig. 13 indicates that the excitability of the vagus is exaggerated after hæmorrhage. There are some facts which suggest that the abnormal excitability is a stage in the progressive failure of the centre, owing to deficient blood supply. The first effect of a fairly large hæmorrhage in the cat is the *rapid*, shallow respiration. This passes into a *slow*, shallow type (Fig. 11) and later still into a very slow but deep

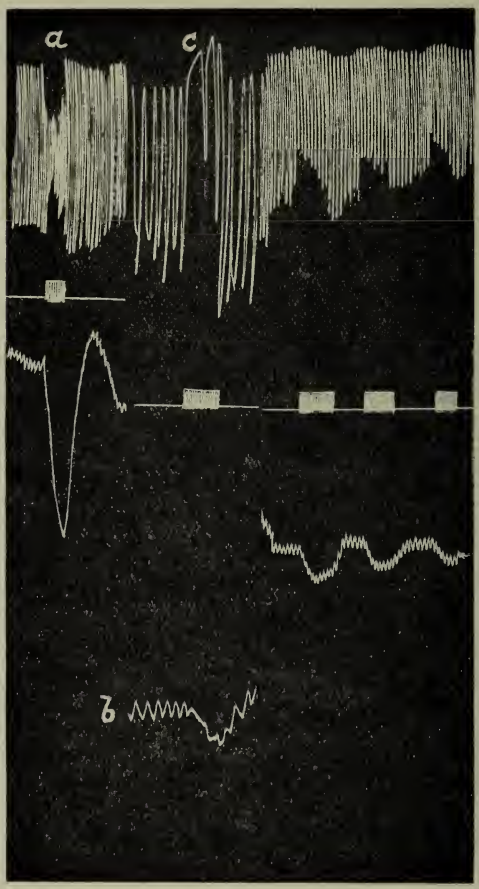


FIG. 13.—**Effect of Hæmorrhage on the Respiratory Reflex from the Vagus.**

Upper curve—respiration.
Lower curve—blood pressure.
Stimulation signal—between the curves.

The strength of the stimulus was adjusted until the rapid, shallow respiration, shown at *a*, was produced. Blood was then removed and the blood pressure fell to the level at *b*. At *c* the same strength of stimulus as before caused a marked inhibition of the respiratory movements. The last three stimulations show a partial return to the first state, after blood had been reinjected. There is a slight quickening of the rate with a decrease in depth. The decrease in magnitude of the depressor reflex on the blood pressure, as the height of this pressure is lowered, may be noted.

type (Fig. 34 below). After muscle injury there may be some other factor in addition to the fall of blood pressure, because the respiratory effect sometimes seems to be out of proportion to the fall of blood pressure, as in Fig. 5. Fig. 14 shows the exaggeration of the injury effect by hæmorrhage.

Another fact that confirms the absence of an increased hydrogen-ion concentration after injection of acid is that the urine collected from a cat during and after injection of relatively large quantities of acid sodium phosphate was not acid to methyl red, although human urine normally is so. There was, perhaps, the very slightest detectable change in the colour towards the acid side, probably due to the small amount of urine secreted before the respiratory centre had brought the reaction of the blood to normal.

We know from Lawrence Henderson's work (1913) that the rise in hydrogen-ion concentration of bicarbonate solutions when partially neutralised with acid is not great because the carbon dioxide escapes. In order to obtain some idea of what the rise might amount to in the blood if the respiratory centre were less excitable than normal, owing to morphine or other influence, so that compensation by removal of more carbon dioxide than normal did not take place, I compared the hydrogen-ion concentration of bicarbonate solutions of the same concentration as in blood, and also of blood plasma itself, before and after neutralisation of one-half of their bicarbonate content by acid. When brought into equilibrium with alveolar air and the tints of neutral red compared, it was obvious that those

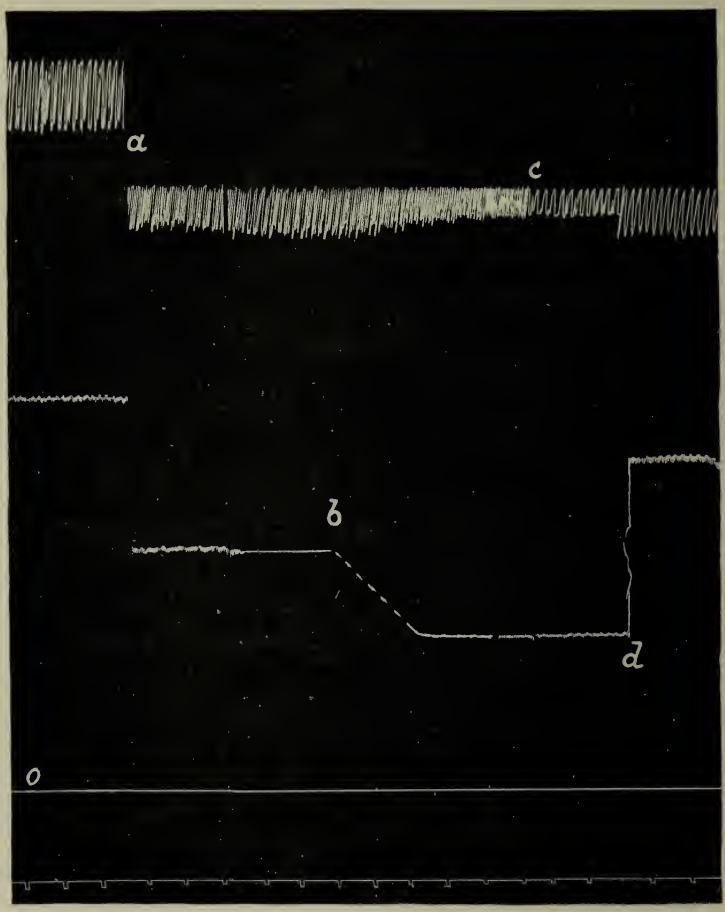


FIG. 14.—**Effect of Muscle Injury and Hæmorrhage on Respiration.**

Upper curve—respiration.
Lower curve—blood pressure.
Bottom line—time in ten second intervals.

At *a*, muscles hammered. Rapid, shallow respiration.

b. Blood removed. Exaggeration of respiratory effect. But later, at *c*, becomes slow and shallow.

Injection of gum-saline at *d* restores the blood pressure and the respiration.

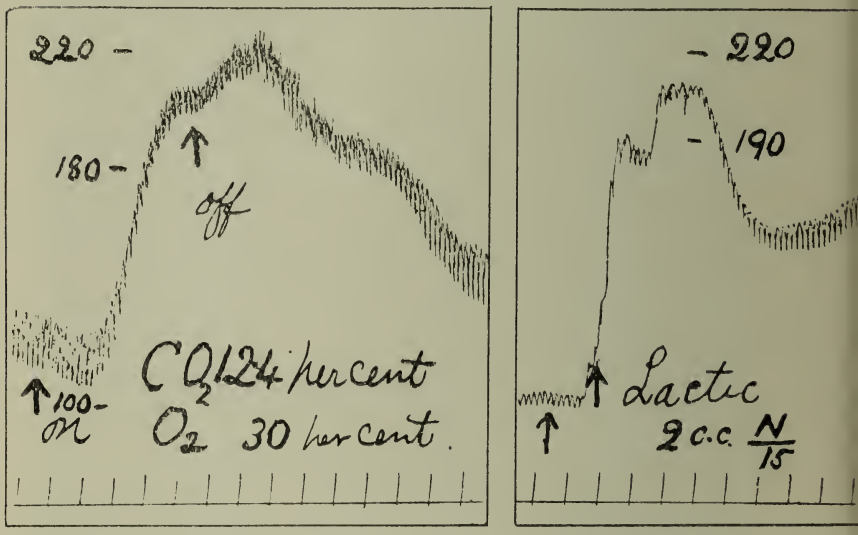
solutions with less bicarbonate were distinctly more acid; the tint was crimson, instead of red. Comparing them with standard phosphate solutions, the hydrogen-ion exponent was found to be, in Sörensen's nomenclature, 6·8 and 6·9 respectively, or, $1{\cdot}58 \times 10^{-7}$ and $1{\cdot}26 \times 10^{-7}$ normal. We may note that the addition of 0·01 gram only of lactic acid to 10,000 litres of an acid of $1{\cdot}26 \times 10^{-7}$ would raise the hydrogen-ion to $1{\cdot}58 \times 10^{-7}$.

I next took the more acid solution and brought it into equilibrium with a carbon dioxide atmosphere of 2·5 per cent., that is about half that of alveolar air. Its colour became identical with the less acid one of the previous test. On the other hand, if the less acid one was exposed to an atmosphere of 8·9 per cent., about 1·5 times that of alveolar air, its tint became that of the more acid. These changes in alveolar tension are well within the power of adaptation of the lung ventilation. Henderson and Haggard (1918, p. 336) point out that to maintain the hydrogen-ion constant when the bicarbonate falls from 63 to 42, 50 per cent. more ventilation only is required; and if it rises from 63 to 84, 25 per cent. less. And they also remark (p. 337) that people living at high altitudes have what must be regarded as a normal hydrogen-ion concentration in their blood, although their alveolar carbon dioxide tension is very different from that of people in low altitudes.

If the respiratory centre fails, then, to compensate, a change of hydrogen-ion represented by that of P_H from 6·9 to 6·8 may occur when the bicarbonate is reduced to one-half. We must examine, therefore,

what effects have been found to be produced by increase of hydrogen-ion concentration.

Stimulation of Nerve Centres.—The respiratory centre is exceptional in its extreme sensibility to hydrogen-ions. The bulbar vaso-motor centres are also excited, but require greater concentration



A *B*

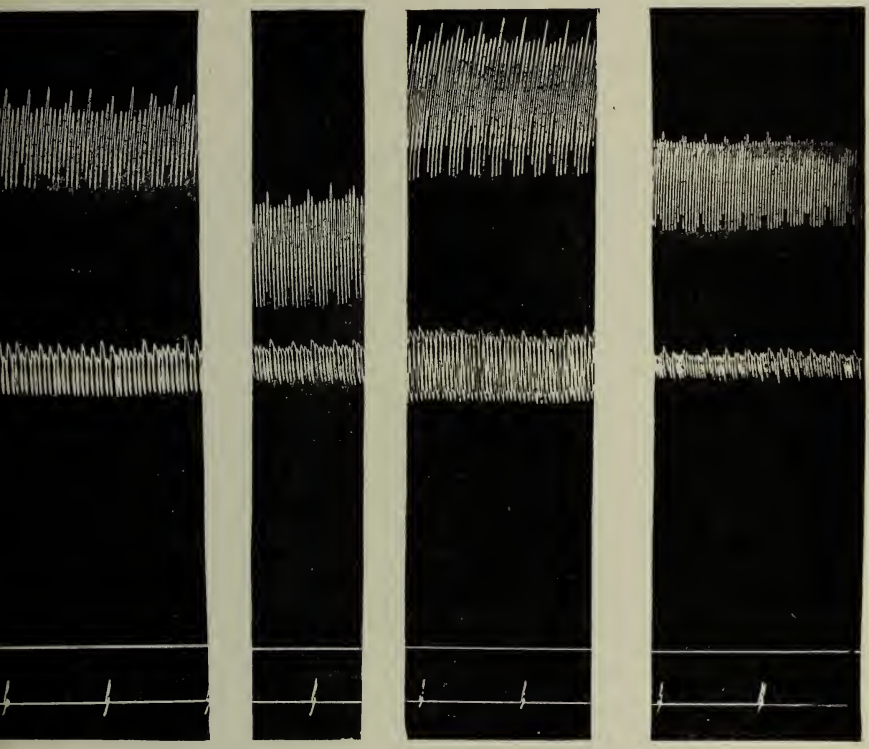
FIG. 15.—Effect of Acid on Vaso-constrictor Centres.

A. On bulb, 2 c.c. of 0·6 per cent. lactic acid into vein.
B. In spinal cat, 8 c.c. of 1·3 per cent. glycollic acid into carotid artery. (Mathison.)

and the spinal centres greater still (Mathison, 1910, 1911) (see Fig. 15).

The effect on the blood pressure of this vaso-constrictor action is counteracted by other effects on the heart and blood vessels (see Fig. 19 below).

The Heart.—Patterson (1915) showed that



I. II. III. IV.

FIG. 16.—**Effect of Carbon Dioxide and Adrenaline on the Heart.**

Upper curves—heart volume. Systole downwards. Rise of general level means increase of heart volume.

Lower curves—arterial pressure.

Heart-lung preparation.

I. Normal.

II. Adrenaline.

III. Carbon dioxide and adrenaline.

IV. Adrenaline.

The combination of carbon dioxide and adrenaline gives greater output than normal, or adrenaline alone.

(Patterson.)

carbon dioxide inhalation depressed cardiac contraction in the dog; but at least 5 per cent. in the air breathed was necessary, while cats were more refractory. According to R. W. Scott (1917), breathing 5 per cent. carbon dioxide raises the P_H of the blood from 7·4 to 7·2, an increase greater than that produced by neutralising half the bicarbonate with acid. We have further to remember that this effect of carbon dioxide was found by Patterson to be counteracted by small amounts of adrenaline (see

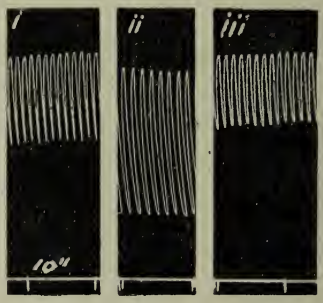


FIG. 17.—Hydrogen-ion Concentration for Frog's Heart.

i. Perfusion fluid with hydrogen-ion concentration of $10^{-10\cdot4}$ N.
ii. Do. do. do. $10^{-7\cdot2}$ N.
iii. Do. do. do. $10^{-10\cdot4}$ N.
CO_2 added to make No. ii.

(Mines, 1913, p. 20.)

Fig. 16), and that Bedford (1917) has shown that in shock there is an increase in the adrenaline content of the blood. The experiments of Mines (1913) show that a very faintly acid reaction is the optimal condition for the heart (Fig. 17). Clark (1913) found that a change from a P_H of 7·7 to one of 6·5 had not much effect on the frog's heart for the first twenty minutes, but decreased the beat in eighty minutes.

The Arterioles.—Gaskell (1880) showed that very weak lactic acid dilated the arterioles. I confirmed this (1901) and found that one part of lactic acid in 10,000 parts of Ringer's solution had about

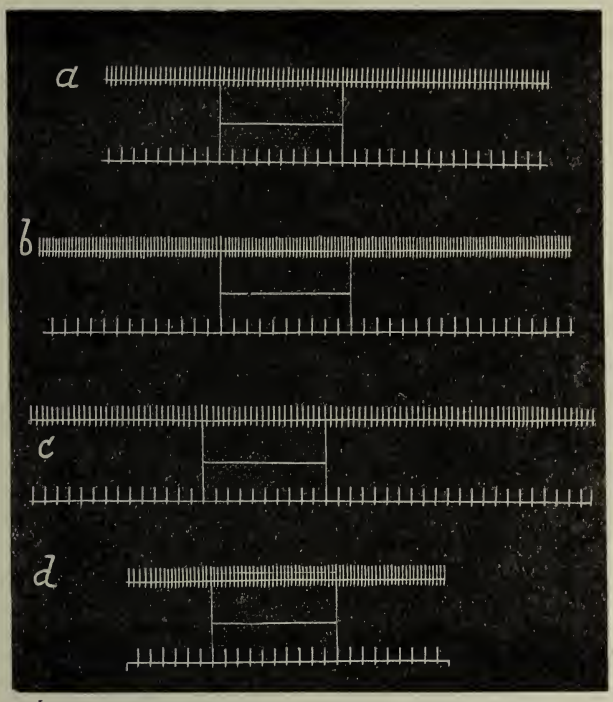


FIG. 18.—Effect of Carbon Dioxide on the Blood Vessels of the Frog.

Hind legs perfused with Ringer's solution. Upper tracing in each gives the drops issuing from the veins. Lower tracing—time in ten seconds.

a. Normal. 25 drops in 100″.

b. Ringer's solution saturated with carbon dioxide. 38 drops in 100″.

c. Normal again. 22 drops in 100″.

d. Carbon dioxide again. 33 drops in 100″.

the same effect as saturation with carbon dioxide, that is, an increase in rate of flow to 1·5 times its

former value (Fig. 18). These concentrations are physiologically high as regards hydrogen-ion concentration and amount to 1,000 times those possible in acidosis. Of course, the local effect of the acid at the point where it is produced is greater than when diluted in the blood, but it is the latter effect that we are considering here. If a small quantity of acid is injected into a vein of the cat, dilatation of the intestinal vessels occurs (Fig. 19). We may note that the effect of acid on the vaso-motor centres has an opposite effect to that on the heart and arterioles.

The Capillaries.—The effect of acid on the capillaries, although of importance in view of the theory that wound shock is associated with stasis of blood in capillary areas, is difficult to investigate owing to the passive changes in the distension of the capillaries owing to dilatation or constriction of the arterioles. Severini (1878) has described dilatation of capillaries in the mesentery when acted on by carbon dioxide, but Roy and Graham Brown (1879) failed to confirm this statement. Dale and Richards found indirect evidence that acid does not dilate capillaries in the fact that section of the spinal cord in the cervical region, after injection of acid, does not give a greater fall of blood pressure than normally. The effect of this section being to cut off the vaso-constrictor impulses from the bulbar centre, so that the arterioles dilate, it would result in a greater fall if the resistance in the capillaries were already low. The arterial pressure remained at about 100 to 120 mm. for some time, in both cases.

The part played by the capillary blood vessels in the phenomena of wound shock is still awaiting satisfactory solution. The experiments of Worm-Müller (1873) led him to believe that additional

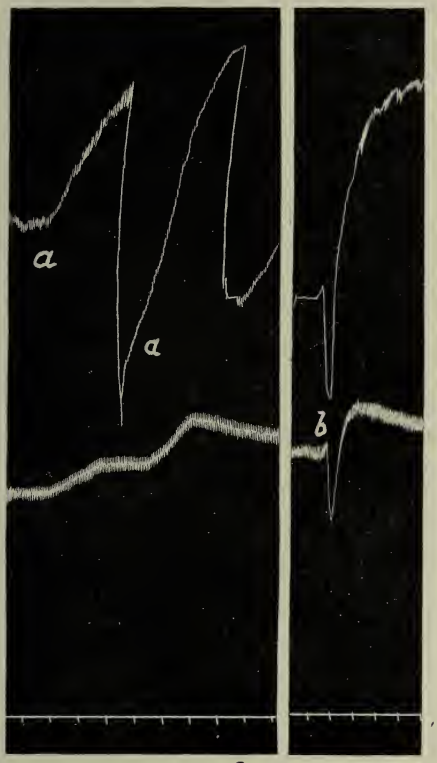


FIG. 19.—**Effect of Lactic Acid on the Blood Vessels of the Cat.**

Upper curve—volume of intestine by plethysmograph.
Lower curve—arterial pressure.
Spinal cord cut just below bulb.

a. About half a cubic centimetre of half molar lactic acid into vein.

b. The same injected more rapidly. The fall of blood pressure is doubtless a direct effect on the heart.

There is some stimulation of constrictor centres in the cord, as shown by the rise of blood pressure, but the intestinal vessels recorded dilate.

blood injected into the circulation is accommodated in the capillaries, chiefly by filling up of those previously empty. An experiment by Roy and Graham Brown (1879, p. 340) is regarded by them as a proof of a dilator effect of chloroform on the capillaries themselves. When chloroform vapour acts on the web of the frog, it is seen to cause widening of both arterioles and capillaries. That of the former might be the indirect cause of that of the latter. The investigators next produce reflex inhibition of the heart, so that the arterial pressure falls to zero. But the capillaries do not empty. It seems to me that the interpretation to be put on this result is not quite clear. If the capillaries are non-elastic, there is no force to empty them, when the arterial pressure falls, after they have been distended by dilatation of the arterioles. If they are elastic, their reaction ought to empty them back into the arterioles when the pressure therein is zero.

If there is a stasis in the capillaries in shock (exæmia), it might be increased by the dilator effect of the acid produced by the tissues, and bicarbonate might assist in the re-establishment of the circulation. But it is not evident that it would do more than a rise of blood pressure would do.

On the general question of the reactivity of the capillaries, independent of that of the arterioles, Dale and Richards (1918), in a recent paper of great interest, bring forward powerful evidence that this actually exists. They point out that a denervated paw of the cat, although warmer than the normal paw, is paler in colour. The flush of the normal paw must be due to distension of the

capillaries by blood, which, however, is moving slowly on account of the relative constriction of the arterioles. These latter may therefore be dilated with a more rapid flow of blood through undilated capillaries. We are reminded of the behaviour of the skin in cold weather. In some persons it may be pale, but warm, while in others it may be red, but cold. Frequently the blood in the capillaries in these latter cases is venous in colour, owing to its slow rate of flow, and then we speak of being "blue with cold." Dale and Richards show by a variety of experiments, for which the original paper must be consulted, that histamine has an opposite action on arterioles and capillaries. It constricts the former, corresponding to its action on plain muscle in general; it dilates the latter. The authors suggest that substances similar in action to histamine may be produced by injury to tissues (see the discussion on muscle injury below).

Effect on the Transport of Oxygen.

Barcroft and Orbeli (1910) showed that increase of hydrogen-ion concentration in the blood causes a change in the form of the dissociation curve of oxy-hæmoglobin, so that, while at alveolar tension of oxygen (about 100 mm. of mercury) there is very little difference in the amount taken up, at lower tensions the amount is notably less and in inverse proportion to the acidity (Fig. 20). For example, by the addition of 0·08 per cent. lactic acid (equivalent to a reduction of the Van Slyke "alkaline reserve" by one-third) the oxygen saturation of hæmoglobin is only reduced to 92 per cent. of the normal at 100

mm. tension, but to 68 per cent. of the normal at 48 mm. tension. This fact has sometimes hastily been

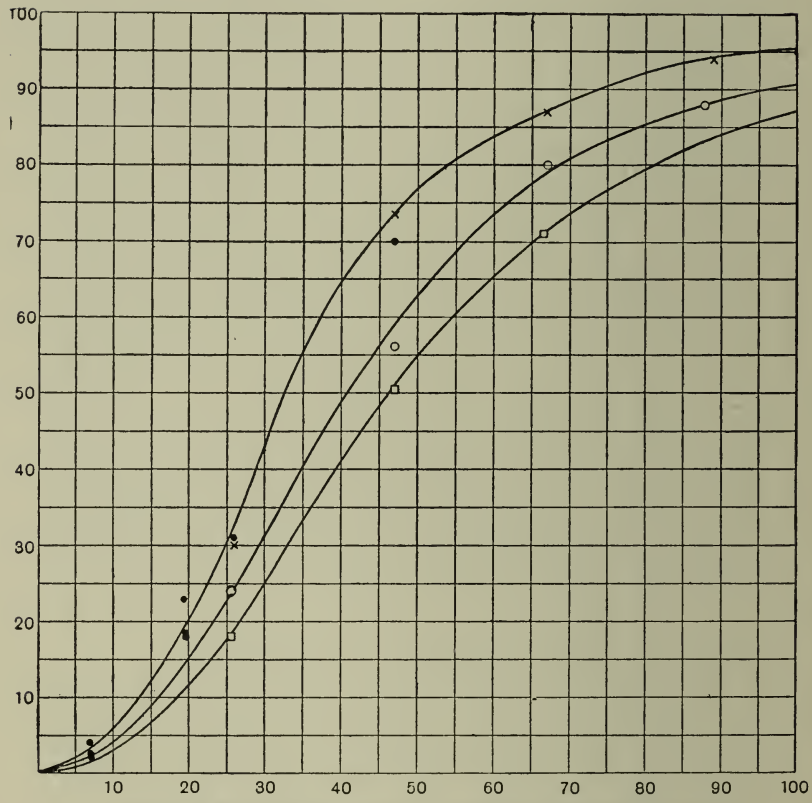


FIG. 20.—**Effect of Lactic Acid on the Dissociation Curve of Oxyhæmoglobin.**

Uppermost curve—normal sheep's blood.
Middle curve—after addition of 0·04 per cent. of lactic acid.
Lowest curve—after addition of 0·08 per cent. lactic acid.
Ordinates—percentage saturation with oxygen.
Abscissæ—tension of oxygen in mm. of mercury.
(Barcroft and Orbeli, *Journ. of Physiol.*, **41**, 360.)

assumed to indicate the harmful effect of an increase of hydrogen-ion. But a little consideration will

show that the contrary is the case. The oxygen content of the arterial blood supplied to the tissues is scarcely altered, but, as this oxygen is used up, its tension in the more venous part of the capillaries decreases, and the effect of the hydrogen-ion in this situation is to *increase* the amount of available oxygen. The oxygen tension in the tissues is proportional to that in the venous blood, and is, therefore, greater in the presence of increased hydrogen-ion concentration. There is thus an automatic increase in the supply of oxygen, as the acid products of the tissues, due to inadequate supply, begin to make their appearance.

Viscosity of Blood.—Statements have been made that acid increases the viscosity of the blood and, on this account, tends to facilitate stasis in the capillaries. Experiments which I made showed no detectable change on saturation with carbon dioxide, nor on the addition of sufficient lactic acid to combine with half of the bicarbonate. The viscosity of blood is difficult to determine accurately and requires many precautions.

Swelling of Red Corpuscles.—Hamburger (1897) showed that the red blood corpuscles swell in the presence of carbon dioxide. But their diameter is not increased, they become more globular in form. This fact may explain why no increase in viscosity is produced.

Swelling of Colloids.—This effect of hydrogen-ion has been brought forward by Martin Fischer (1910) as playing an important part in a variety of physiological processes. It has been suggested that acidosis might cause swelling of the walls of the

capillaries, or perhaps of surrounding tissue cells, and so lead to obstruction of blood flow. The figures given by Fischer and G. Moore (1907) show that fairly strong acid is necessary to produce any marked effect on colloids. $\frac{1}{80}$ N. lactic acid has practically no effect on the swelling of fibrin, and muscle was found to behave similarly. The volume assumed in water being 6, that in $\frac{1}{80}$ N. lactic acid was 7, in $\frac{1}{10}$ N.—28. The former has a hydrogen-ion concentration of about 10^{-2} N., that is, more than 10,000 times as great as that of "acidosis."

Oxidation Processes.—Some of these reactions, not all, are retarded *in vitro* by increase in hydrogen-ion. Warburg (1910) showed that sodium hydroxide in 10^{-4} N. concentration doubles the oxygen consumption of developing eggs of the sea urchin. Here again we are dealing with a concentration far beyond those possible in the blood. The mechanism of oxidation in cells is obscure, and it is clear that lactic acid is rapidly oxidised by the muscle cells in an acid medium, provided that oxygen is supplied in due amount.

Diabetes.—Hasselbalch showed (1912) that, in the so-called "acidosis" of carbohydrate starvation, the hydrogen-ion concentration of the blood remains unaltered. Any increase of acid circulating in the blood is compensated for by a diminution in the carbon dioxide content.

Although there is frequently a low value of bicarbonate, there is a normal blood pressure and the condition has no resemblance to that of shock. Poulton (1915) has shown that in diabetic coma, although there is undoubtedly decrease of bicar-

bonate (Stillman, Van Slyke, Cullen, and Fitz, 1917), there is no increase of hydrogen-ion concentration. One case may be quoted: the alveolar carbon dioxide tension was only 12 mm., indicating a very

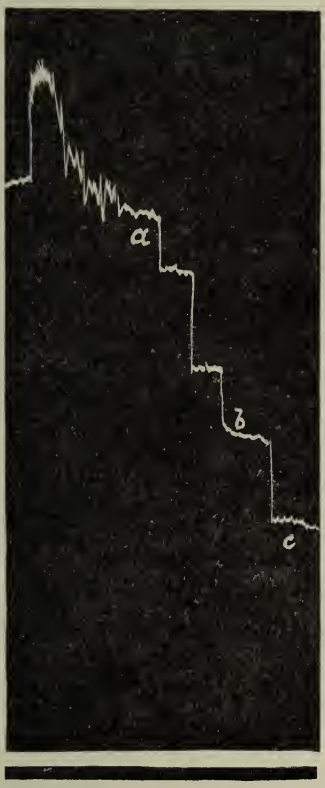


FIG. 21.—Fall of Blood Pressure produced by Acid Injection.

Decerebrate cat. 5·2 c.c. of half-normal hydrochloric acid per kilo had been injected into a vein before the tracing begins. The secondary fall began at *a*, half an hour after the acid had been given. The level *b* was reached eighteen minutes later. At this time the bulbar centres were capable of reflex stimulation, so that it does not appear that intracranial hæmorrhage had taken place in consequence of the decerebration and affected their functions. Before *c*, half an hour after *b*, a further small dose of acid had been given.

marked production of fixed acids, but it was low enough to compensate and the hydrogen-ion concentration was normal (7·33). Nevertheless, the patient died in coma eighteen hours later. Therefore, the pathological symptoms must be due to some indirect action of the products of insufficient oxidation of fat, not to the acids *quâ* acids.

The Experimental Injection of Acids.—In certain experiments made in conjunction with Major Cannon, we found that the injection of sufficient acid to neutralise one-third of the bicarbonate was sometimes, not always, followed by a progressive fall of blood pressure, accompanied by a steady further decrease in the bicarbonate reserve. In later work, however, I was unable to obtain the fall except in cats obviously unhealthy. Fig. 21 illustrates the shock-like effect; Fig. 22 the absence of such effect.

Results obtained by Dale and Richards show that the fall of blood pressure obtained by Cannon and myself cannot be ascribed to the effect of the acid by itself alone. A large amount of acid can be injected into cats under ether without any fall of blood pressure or other signs of shock. The Van Slyke number may fall below 5 without the animals being any the worse, so far as could be seen. In fact, they recovered from the anæsthetic and ran about just as usual. Recent experiments that I have done myself have compelled me to admit that there was some unknown factor present in the former experiments. I find that, in healthy cats, even under urethane, the injection of acid is innocuous. If it is run in rather rapidly, there is a

temporary fall of blood pressure, but this soon passes off, and the usual result is a rather prolonged rise of blood pressure, with no other symptoms. The only explanation that I can suggest is that the former experiments were done under some stress of

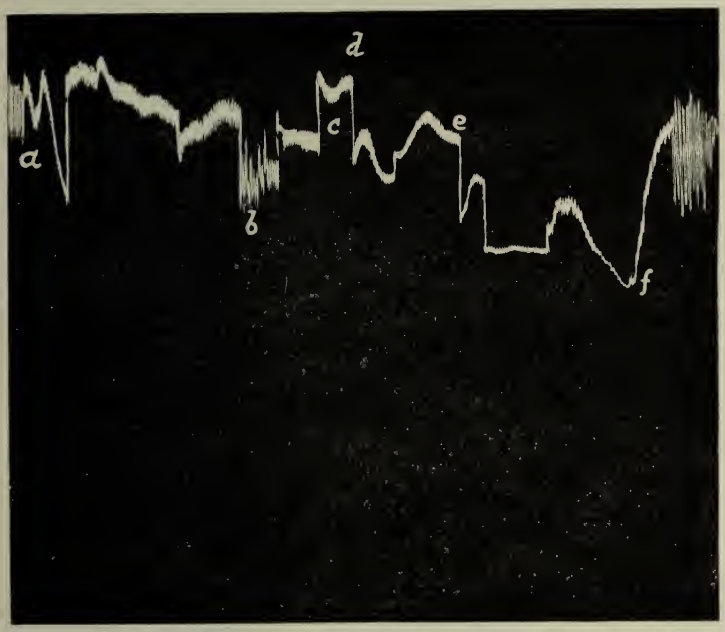


FIG. 22.—**Acid without Effect, until Hæmorrhage was Produced.** Under urethane.

a. Acid given as in Fig. 21.
b. An hour and a half later. Blood pressure, 120 mm.
c. Three hours after injection.
d. Ten c.c. of blood removed (=9 per cent.), and at *e* another 10 c.c.
f. Twenty c.c. gum-saline given, twenty-eight minutes after *e*.
One hour and twenty minutes later, blood pressure normal

time, so that cats were used very soon after their reception at the laboratory. I have noticed that

the animals improve greatly in health and vigour after remaining in the laboratory for a few days, during which they are well fed. In cats obviously unhealthy, there is no difficulty in obtaining a fall of blood pressure which begins during the injection and increases progressively during the succeeding hours. As would be expected, the initial fall can be brought back to normal by neutralisation of the acid by injection of bicarbonate. But this cannot be done at a later stage, and at this stage, even blood transfusion is of no use. Some secondary process, probably due to the low blood pressure, has set in, which is not directly due to the acidosis present at the time.

Experiments have been described by Spiro (1902) and others in which hydrochloric acid was put into the stomach of rabbits, or sodium hydrogen phosphate into the circulation of dogs, with "shock" effects. I have repeated the experiments with acid phosphate on cats and found no difference between the action of neutral and of acid phosphate in equal amount. Both produced a moderate fall of pressure, which I am inclined to attribute to the hypertonicity of the solutions. At all events, it was not improved by injection of bicarbonate, although brought back by gum.

I may remark here that my experiments indicate that great care must be exercised in the intravenous injection of any hypertonic solution. I have seen even sodium bicarbonate in 4 per cent. solution produce a serious progressive fall of blood pressure, which was, however, rather to my surprise, brought back effectively by gum-saline.

While acid injections of themselves do not appear to be injurious, and I may here refer to an apparently paradoxical experiment in which muscle injury had produced a marked fall of blood pressure with other signs of "shock," but in which injection of lactic acid caused recovery, they are very liable to make the animal more sensitive to loss of blood, so that a loss of 20 per cent., which would have no serious effect on a normal cat, may result in a progressive and continuous fall of blood pressure. That the action of acid here is to exaggerate that of hæmorrhage, rather than vice versa, is suggested by the fact that this secondary state is more effectively treated by injections of gum than by bicarbonate (see Fig. 23). Dale and Richards have noticed that the shock-producing action of histamine is increased by acid, while that of peptone is not. An animal may, however, recover from histamine shock without any rise in the bicarbonate reserve.

On the whole, it would seem that the existence of a decreased reserve of bicarbonate is not to be regarded as, in itself, dangerous. What it indicates, when present, is that the blood supply to the tissues has been inadequate to ensure a sufficient supply of oxygen to them. Hence, I venture to think, the more rational treatment is to increase the oxygen supply by an improved circulation, rather than to neutralise the acid after it has been produced. Major Cannon has found recently that, in laboratory experiments, after a fall in the bicarbonate reserve has been brought about by a low blood pressure, the raising of this pressure by a gum-saline solution causes a return of the bicarbonate to or towards the normal

level. I may also mention that experiments done by Major Cannon and myself showed that breathing of air deficient in oxygen results in decrease of bicarbonate, while that of a mixture of carbon dioxide with excess of oxygen does not.

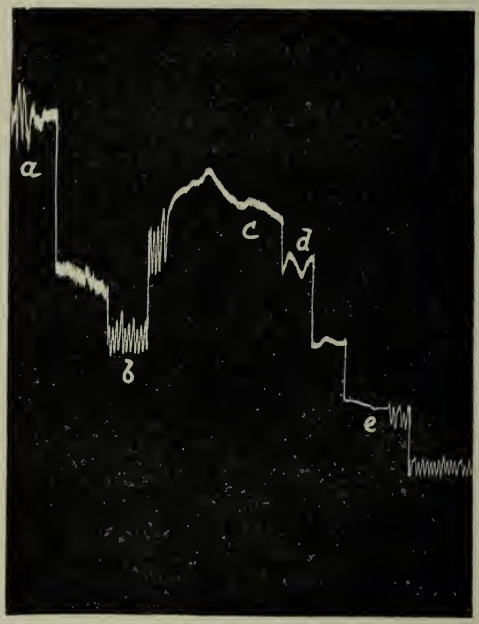


FIG. 23.—**Failure of Bicarbonate after Acid Injection.**
Cat under urethane.

a. Acid given.
b. Sodium bicarbonate equal to acid given.
c. Rebreathing (through 44 cm. tube). (Bicarbonate reserve = 48.)
d. Rebreathing stopped.
e. Half an hour later. (Bicarbonate reserve = 30.)

I should be inclined to go so far as to regard the increase of hydrogen-ion concentration, which results from formation of fixed acid in the tissues, as an appropriate stimulus to the respiratory centre to

increase ventilation and supply more oxygen. The question arises as to whether in some cases of wound shock, as Dr Haldane has suggested, the inhalation of oxygen might not be combined with gum injections to the advantage of the patient. I would agree with Prof. Yandell Henderson in looking upon "acapnia" as injurious, not because of the loss of carbon dioxide as such, but because the respiratory centre may be deprived of its normal stimulus, and want of oxygen occurs, unless fixed acids are produced. One may regard the increase in lactic acid content of the blood at high altitudes as a compensation for decreased alveolar carbon dioxide tension, and it would scarcely be justifiable to call it "acidosis," although it involves a decrease in bicarbonate reserve.

Cannon's determinations of blood pressure and alkaline reserve in wounded men (1917, pp. 42 *seq.*) showed generally that the lower the blood pressure, the lower the bicarbonate value. On comparing the figures, he finds that, from about 70 mm. of mercury blood pressure downwards, a rapid decrease of bicarbonate reserve occurs. The average numbers are as follows :—

Blood Pressure	Average CO_2 Capacity.
Above 80	49
70-80	43
60-70	35
Below 60	27

He concludes that if the systolic pressure does not rise above 80 mm., on rest and warmth, measures must be taken to raise it by intravenous injection.

An acidosis as great as that in shock, as Cannon points out (p. 50), may occur after muscular exercise. But, under normal conditions, oxidation processes and urinary secretion rapidly remove it. These processes, we may note, are directly dependent on a good blood pressure. The existence of acidosis does not imply shock ; as is also evident from what we have seen above in connection with diabetes and with life at high altitudes. The low blood pressure of shock is the cause of the "acidosis." Milroy (1917) showed that hæmorrhage, and Dale and Richards that low blood pressure due to section of the spinal cord, result in decrease of the bicarbonate reserve.

Erlanger and his colleagues (1918) find the bicarbonate reserve irregular in shock and not the primary cause. Guthrie (1918) comes to the same conclusion. The degree of "acidosis" would naturally depend on how long the blood pressure had been at a low level. Henderson and Haggard (1918, p. 344) found that the carbon dioxide capacity goes up steadily during the rebreathing of expired air, but the animal may die when fresh air is admitted. Under morphine, although the respiration is defective, the carbon dioxide capacity goes up. Under ether, it may either increase or decrease (pp. 350-351), but in both cases the dog under experiment died with dark blood. The interchange of base between corpuscles and plasma, as shown by Hamburger, plays a part in these phenomena ; but the discussion of this factor does not fall within the scope of the present inquiry.

So far from the acidosis of shock being a state to be combated, it would appear that it might even

be sometimes increased with advantage by breathing air containing a slight excess of carbon dioxide, as recommended by Yandell Henderson and by Porter. But, since the object is to increase oxygen supply, it must not involve decrease of oxygen, as would be the case if expired air were rebreathed. It might perhaps be thought that increase of carbon dioxide in the arterial blood would affect prejudicially the taking up of oxygen. But the curve of Barcroft (Fig. 20) shows that, at the oxygen tension of alveolar air, that is, of arterial blood, increase of hydrogen-ion has very little effect until it becomes excessive. On the other hand, Cannon thinks that the blood in wound shock is usually fully oxygenated, so that there is no need to stimulate the respiratory centre. The tissues suffer because the blood supply is not rapid enough.

If we accept the conclusion that an increase in hydrogen-ion concentration may be of benefit, it follows that alkaline injections cannot also be advantageous. The possible improvement of the capillary circulation must not be forgotten as a point in favour of alkaline treatment, although it is not an established fact.

In experiments on cats, I found bicarbonate to be comparatively useless, not only in the low blood pressure of hæmorrhage, but also in that of muscle injury, excess of ether, from injection of acid phosphate, or from cold in combination with slight hæmorrhage.

Too low a hydrogen-ion concentration is as bad as too high a concentration. There is an optimal one both for respiration and for the heart, as well

as for other physiological processes. I have seen experimentally that the introduction of bicarbonate may lead to a depression of respiration so far that the blood became very dark and artificial respiration was necessary to supply oxygen. The organism, so far as my experiments go, can accommodate better to increase of acid than to that of alkali. I gave to a normal cat an amount of bicarbonate equivalent to that of the hydrochloric acid to which the cat so far accommodates as to keep the hydrogen-ion constant. Before the bicarbonate, the plasma gave the normal orange tint with neutral red. One hour after the injection, the plasma gave a distinctly yellow tint, showing that the hydrogen-ion reduction had not been compensated. In another case, in which also bicarbonate was injected into a normal cat, there resulted a progressive fall of blood pressure, which was, curiously enough, cured by an injection of gum-saline (see Fig. 56). For these reasons, the use of the more alkaline carbonate is especially to be deprecated, although it has been recommended. In one of my experiments, an injection of 6 per cent. gum containing 2·5 per cent. of sodium carbonate did not raise the pressure after hæmorrhage as high as the gum usually does, and it showed a steady fall afterwards. A dose of lactic acid raised it permanently.

We finally arrive at the conclusion that such an "acidosis" as is sometimes present in wound shock is innocuous in itself and may even be beneficial in increasing the supply of oxygen by greater pulmonary ventilation. The use of alkaline injections is unnecessary. They are of no more value than

other simple salt solutions for raising the blood pressure after hæmorrhage. Although Sir Almroth Wright (1918) correctly points out that the "acidæmia" of shock is due to defective oxidation, he fails to draw the obvious conclusion that the treatment is to raise the blood pressure. The mere injection of bicarbonate solutions, as he advises, is practically useless. If an animal is bled to such a degree that it will die without treatment, injections of bicarbonate solutions will not save it; whereas gum-saline, as we have seen, will do so. Moreover, if we exaggerate the "acidosis" by introducing lactic acid, bicarbonate alone is ineffective, whereas gum alone is curative (see Figs. 24 and 25).

The sterilisation of bicarbonate solutions is difficult, because they become too alkaline by loss of carbon dioxide, unless closed. The solid bicarbonate may be heated in closed capsules and dissolved in sterile distilled water. If, for other reasons, bicarbonate is considered to be desirable, it may be given by stomach or rectum. Milroy (1917) shows that it is rapidly absorbed from the rectum.

At the risk of tiresome iteration, I would again emphasise the importance of *adequate oxygen supply* to the tissues. Evidence from various sources is repeatedly turning up which impresses this fact upon us more and more. I may refer briefly to some of these.

After inhalation of *pulmonary irritant gases*, such as chlorine or phosgene, breathing of oxygen has shown itself to be by far the most effective mode of treatment. Although it was insisted upon

by Haldane from the first, it fell for a time into disfavour because of the temporary discomfort caused by it in some cases. It appears that after prolonged asphyxia, the nerve centres become more or less insensitive, so that the patient, although blue, is not dyspnœic, and does not feel distressed.

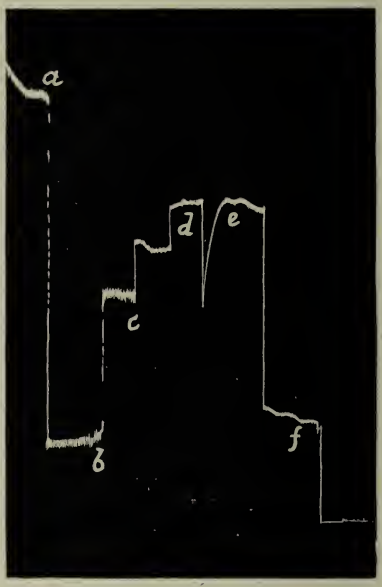


FIG. 24.—**Failure of Bicarbonate to Cure "Acidosis" and Hæmorrhage.**

a. Bled 28 per cent.
b. Lactic acid into vein, 13 c.c. of half-normal.
c. Sodium bicarbonate, 15 c.c. of half-normal, and 13 c.c. of Ringer's solution. Together equal to the volume of blood withdrawn.
d. Forty-five minutes after bleeding.
e. One hour after bleeding. Occasional respiratory gasps. Rise of blood pressure probably asphyxial.
f. One hour and twenty minutes after bleeding. Heart stopped eleven minutes later.

This state is extremely dangerous, and would soon end in death. The first effect of the supply of

oxygen, which is imperatively necessary, is the restoration of sensibility to the nerve centres, so that the patient feels his distress and objects to the oxygen. But, if continued, relief is obtained, and the life of the patient may be saved.

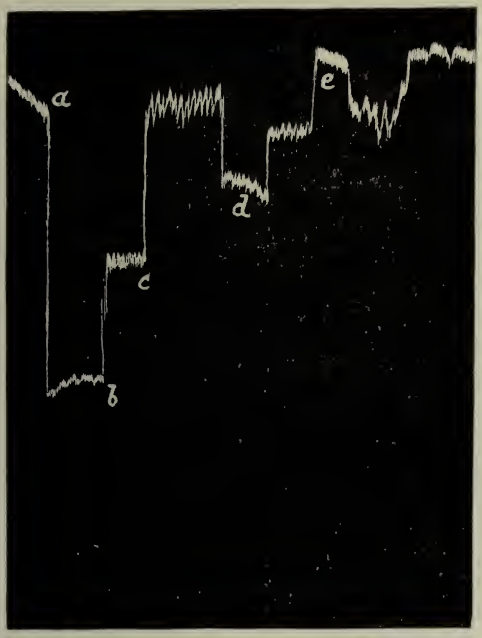


FIG. 25.—**Cure of "Acidosis" and Hæmorrhage by Gum-Saline.**

Experiment similar to previous figure, but gum given instead of bicarbonate.

a. Bled 37 per cent.
b. Lactic acid, 12 c.c. of half-normal.
c. Gum-saline, 41 c.c. (equal to volume of blood withdrawn).
d. One hour and twenty minutes after bleeding.
e. Two hours and forty minutes after bleeding. Blood of a good colour.

Final tracing—four and a half hours after bleeding.

Anæsthetics. — Marshall (see Cannon, 1917, p. 69) insists on the necessity of avoiding anything

like asphyxia, and points out the great value, for this reason, of nitrous oxide and oxygen. In experiments on cats, I have found it difficult to maintain anæsthesia with ether without more or less darkening of the blood, however carefully the ether is administered.

Rebreathing Expired Air has been recom-

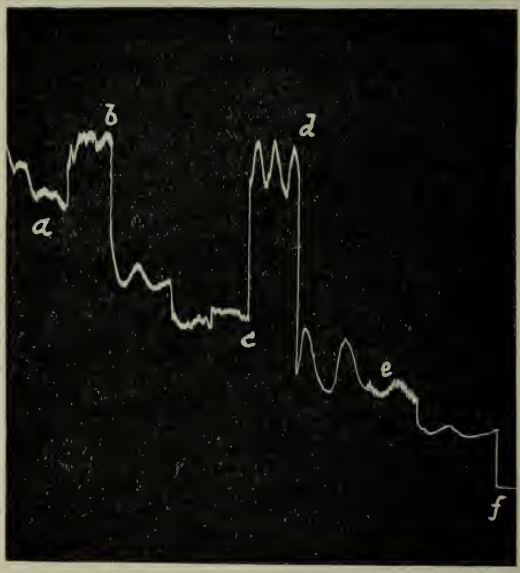


FIG. 26.—**Rebreathing Expired Air.**
Cat under urethane.

a. Started rebreathing by attachment of a wide tube, 166 cm. long, to tracheal canula. (Bicarbonate reserve = 54.)
b. Tube off after twenty-three minutes.
c. Tube on.
d. Tube off again after twenty minutes.
e. Forty-five minutes later. (Bicarbonate reserve = 35.)
f. One hour after *e*.

mended by Porter and by Yandell Henderson as a treatment for wound shock. As we have seen,

there may be some advantage in adding a small quantity of carbon dioxide to the air breathed. But a number of experiments made by Cannon and myself showed that expired air itself is very deleterious, no doubt because of its deficiency in oxygen (see Fig. 26). If, however, carbon dioxide is used,

FIG. 27.—**Effect of Carbon Dioxide on the Blood Pressure.**

a. A small amount of carbon dioxide allowed to pass into side of trachea canula through a capillary tube attached to a Kipp generator.
b. Carbon dioxide stopped after forty-six minutes action.
c. Five minutes later.
d. Twenty-six minutes after carbon dioxide.
e. Ten minutes later.
f. After 9·5 c.c. of half-normal hydrochloric acid into femoral vein.

great care is necessary not to exceed a minimal amount, since it produces a fall of blood pressure, which may be great, although temporary (Fig. 27).

Glucose Solutions.—These have sometimes been recommended on the idea that there may be carbohydrate starvation in wound shock. In such a state, fat is imperfectly oxidised, so that oxybutyric and aceto-acetic acids appear in the urine. Cannon (1917, p. 52) found, on the other hand, as would probably be expected, that the blood sugar is above normal in shock and has no relation to the decrease of bicarbonate reserve. No "acetone bodies" were present in the urine. The "acidosis" of diabetes is of quite a different origin from that of shock.

Rous and Wilson (1918) found a 5·4 per cent. solution of glucose to have only a slight transitory effect in raising the blood pressure in rabbits after hæmorrhage.

There is therefore no object in adding glucose to solutions for intravenous injection.

LECTURE II

We have seen that the effect of solutions containing salts, or other crystalloids, alone is very transitory. Any of the solutions referred to in the preceding lecture may produce some temporary rise of blood pressure. But this usually disappears in less than half an hour and is likely to be followed by a greater fall than the original one.

We saw also that such solutions are defective in two respects :—

1. Their viscosity is too low, and
2. They contain no colloid with an osmotic pressure.

Of these two, *the second is the more important.*

We have next to inquire what substances can be added to remedy these defects.

Strong solutions of *glucose* or *glycerin* have a sufficient viscosity, but, being diffusible, the osmotic pressure inside and outside of the blood vessels rapidly equalise and there is then no force effective to keep the fluid inside. Moreover, solutions strong enough have a deleterious action on the heart and blood corpuscles.

Starch and *Agar* are indiffusible, but their molecular aggregates are so large that the osmotic pressure that they possess is so small as to be scarcely capable of detection.

Fortunately, most of those colloids which possess an osmotic pressure form solutions of a comparatively high viscosity. Several possible ones suggest themselves at once, such as dextrin, proteins, gelatin, and gum acacia.

Dextrin.—We need an osmotic pressure of not less than 30 to 40 mm. of mercury, that of the blood colloids. A solution of dextrin of about 4 or 5 per cent., differing in individual samples, has such an osmotic pressure; but its viscosity is not much higher than that of Ringer's solution. The experiments that I have made with it are not very favourable. Although better than saline, it has a much less permanent effect than gelatin or gum. Possibly the blood vessels are not quite impermeable to it. The dimensions of its molecular aggregates are smaller than those of proteins or gum. Unless the pure material, precipitated by alcohol, which is somewhat costly, be used, it is liable to contain both unaltered starch and also sugar, the latter from too much hydrolytic change.

Rous and Wilson (1918) found 8 per cent. dextrin to have only a transient effect.

Proteins.—Since it is almost entirely to proteins that blood owes its colloidal osmotic pressure, it might hastily be supposed that we might use serum proteins, egg albumin, or even casein. There are, however, two fatal objections. Foreign proteins affect the kidney, so that they appear in the urine. And they produce anaphylactic sensibility, so that, if at any future time, another similar intravenous injection were made, severe anaphylactic shock would almost certainly occur. It must be

remembered that wounded men have already received a dose of anti-tetanus serum, that is, horse serum, and it is undesirable to run an additional risk of anaphylaxis. Cases of anaphylactic shock have occurred, especially when a second dose of tetanus antitoxin is given intravenously without previous desensitisation by a small dose. Intramuscular or hypodermic injection involves little risk, although a mild attack may occur. I happened to see an interesting case at No. 33 Casualty Clearing Station. A wounded man was brought in a short time after the injury. When brought to the surgeon for operation, about an hour later, his appearance had changed completely, owing to marked œdema of the face. The condition was not serious, however, and next morning was normal again.

We are left with gelatin and gum. It is somewhat remarkable that both of these substances in concentrations which have the correct osmotic pressure have also a viscosity almost identical with that of blood. These are 6 per cent. for gelatin, 7 per cent. for gum arabic, when the osmotic pressure is measured in the presence of the salts of Ringer's solution. Against distilled water they have a higher osmotic pressure. The lower osmotic pressure in the presence of salts is probably to be explained by the unequal distribution of the salts between the two sides of the membrane, so that the concentration of salts is slightly higher on the outside, as worked out by me in the case of congo red (1911, p. 249). In most respects there is little to be said in preference of gelatin or gum, but gelatin has certain disadvantages which gum does

not possess. Perhaps, in the requisite degree of purity, gum has the advantage of being cheaper.

Gelatin might seem the more natural, as it is a constituent of animal tissues; or rather, its precursor, collagen, is. It is presumably slowly converted into amino-acids, when introduced into the blood, and thus utilised as food.

Hogan (1915) suggested its use on account of its power of taking up water by imbibition. He states that 2·5 per cent. is capable of holding in chemical combination all the water in the plasma. This is not correct. Water is lost from the blood until the concentration of the gelatin is about what it would have been if a 6 per cent. solution had been used. In other words, the injection of 500 c.c. of 2·5 per cent. solution is only equal in effect to 210 c.c. of a 6 per cent. solution. Hogan did not realise that the factor required is the osmotic pressure. If 2·5 per cent. holds all the water in combination, such a solution ought not to cause hæmolysis of red blood corpuscles, as it actually does. Starch holds water in the same way, but has no effect in keeping water in the blood vessels, because its osmotic pressure is only minimal, as remarked above. A 5 per cent. solution of soluble starch in Ringer's fluid allowed the blood pressure to fall to its original value (58 mm. of mercury) in about an hour.

Rous and Wilson (1918) tested a gelatin solution made up according to Hogan's formula, and found the blood pressure to return to its original level in fifteen to twenty minutes. A 6 per cent. gelatin, on the other hand, had a permanent effect.

It is as well to remark here that the osmotic

pressure of any of the colloids mentioned is not in itself high enough to prevent hæmolysis of red corpuscles. The colloids must be dissolved in 0·9 per cent. sodium chloride. The cell membrane is impermeable to this salt, contrary to the wall of the blood vessels, so that its osmotic pressure is effective in the former case.

Owing to the source of most of the best commercial gelatin, namely, calves' feet, it is liable to contain the spores of tetanus bacilli, which are difficult to kill. Accidents have happened in the past from this cause. If sufficiently sterilised, gelatin loses much of its viscosity, although it has been stated that this does not occur in the presence of salts. But a sample sent to me after the treatment had actually lost a great part of its viscosity although not so much as in the absence of salts.

Another unwelcome property of gelatin is that of causing intra-vascular clotting. At one time it was injected into the sacs of aneurisms with this object. Dale observed that a rabbit died on the second day after an injection of gelatin, with a clot in the right heart. It is not quite certain, however, whether the solution had been sufficiently sterilised. I have not noticed any unpleasant effects in the course of two or three hours. According to Schmerz and Wischo (1918), the action of gelatin on the coagulation of blood is due to its adsorbing calcium salts from the blood; but it is not clear why this should not have the opposite effect.

In cold weather, the setting to jelly in the tubes and canulæ, if a block occurs, may become inconvenient.

Fortunately, gelatin has no properties of importance for our purpose that gum does not possess, and we may now pass on to the more detailed consideration of the properties of solutions of gum arabic.

GUM ARABIC

A solution of 6 to 7 per cent. in 0·9 per cent. sodium chloride has the viscosity of blood and the osmotic pressure of its colloids. Hence such solutions do not leave the blood vessels (Figs. 28 and 29).

The fact is also shown by perfusion of organs with these solutions. The absence of œdema is striking and I can highly recommend the substitution of gum solutions in Ringer for routine use in such experiments, instead of the usual simple saline or Ringer's solutions. Probably a more dilute solution than 6 per cent. would be better for the frog ; but we do not know the osmotic pressure of the colloids in its blood.

Gum is quite innocuous, as might be expected from its chemical inertness. Dale has tested it in rabbits and I have done so myself in cats. In one case I kept a cat for three weeks after an intravenous injection of 7 per cent. gum in volume equal to nearly half its calculated blood volume. Meek and Gasser (1918) gave enough to make the blood contain 10 per cent. of gum, without ill effects. Drummond and Taylor (1918), in an experience of some 250 cases, found it harmless in man. In cases that died from wounds, after injection, no thrombosis or other lesions dependent on the gum were met with.

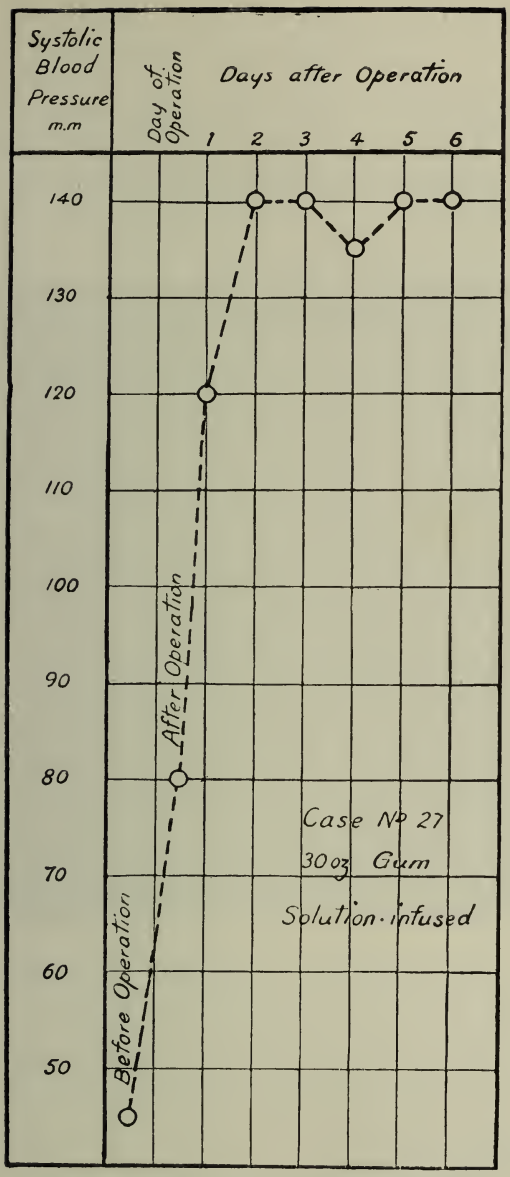


FIG. 28.—**Gum-Saline in Wound Shock.**

Case of abdominal shell wound. Apparently moribund on admission. On operation, two pints of blood in peritoneal cavity. Six perforations of intestine sutured. Intravenous injection of gum during operation. At end of operation (thirty minutes)—blood pressure, 80 mm. and fair pulse. Next day—blood pressure, 120 mm. and later 140 mm., remaining permanently.

(Fraser and Cowell, 1917, p. 22.

Properties.—The solutions are easily sterilised without loss of viscosity. The temperature of a steam steriliser was sufficient for the experiments which were made on cats, although it might be

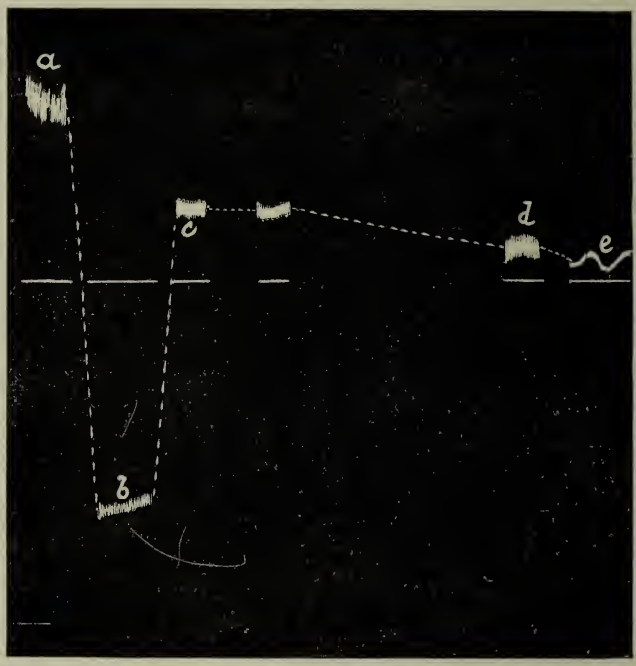


FIG. 29.—**Gum Solution (5 per cent.) after Hæmorrhage in Cat.**

a. Initial height of blood pressure (zero at base of figure). Horizontal line marks 100 mm.
b. After 66 per cent. of the blood had been removed in three stages.
c. After replacement of the blood lost by gum arabic in saline. Note that the viscosity is not sufficient to raise the pressure to its original height.
d. After 2·5 hours.
e. After three hours.

The tracings are spaced in order to compare with Fig. 9.

safer to use an autoclave. Solutions exposed to the air do not easily grow moulds or bacteria,

probably because of the absence of nitrogenous compounds.

Since they do not contain protein, it is unlikely that *anaphylaxis* would be produced. But it seemed best to test it. Cats and guinea pigs received intravenous injections three weeks after a previous injection without showing any signs of anaphylactic shock.

Govaerts (1917), in his studies of post-hæmorhagic anæmia, found what he calls "artificial serum" of scarcely any value compared with transfusion of blood. But his solutions were simple saline solutions and the results merely serve to confirm what we have found above. This observer rightly points out that what is necessary is to increase the volume of the circulating blood; but, although he suggests that the addition of an appropriate colloid might serve the purpose as well as blood, he objects to the use of foreign colloids on account of their toxic character. The risk is no doubt present with proteins, but Govaerts is apparently unaware that it had been shown to be absent with gum. Indeed, the natural conclusion to be drawn from his results is that a liquid containing gum would be as effective as blood.

Tested for *hæmolytic and agglutinating properties*, these were found to be absent with human blood. But, if an excess is added to cat's blood, the corpuscles appear to be agglutinated and sink quickly. Whether this is a true agglutination seems doubtful, because if the sedimented corpuscles are injected into a vein, no harm results. If the sediment is shaken up with the supernatant fluid, the corpuscles are completely resuspended, and are evidently very

loosely held together. It may be that in the circulation the continual movement prevents this "agglutination" in the whole animal, but it is more probable that the explanation lies in the fact pointed out by Captain O. Robertson (1918, p. 8), in connection with transfusion of blood. It is found to be of no consequence if the plasma of the donor agglutinates the corpuscles of the recipient *in vitro*. This does not happen *in vivo* because of the dilution of the donor's blood, together with the protection afforded to the red corpuscles of the recipient by their own plasma. But, nevertheless, the "spurious agglutination" in the cat does actually happen *in vivo*, in the sense that blood drawn after an injection of gum deposits its corpuscles more rapidly than normally. I gave a volume of 6 per cent. gum equal to 27 per cent. of the animal's blood. A sample of blood taken, and mixed with a small quantity of oxalate, was found to settle about three times as quickly as a sample taken before the gum was injected. This is clearly not a matter of decreased viscosity, because, although 6 per cent. gum is about equal in viscosity to whole blood, its viscosity is higher than that of plasma. Since there is abundant evidence that this kind of agglutination is quite harmless to the cat, the question naturally arises as to whether the agglutination produced by some kinds of foreign serum *in vitro*, in the case of human blood, may not actually occur *in vivo*, but be of no consequence, apart from hæmolysis. It would be of interest to know whether a sample of blood taken from a man who has had a transfusion of blood, the plasma of which was found to agglutinate the recipient's cor-

puscles *in vitro*, shows any signs of agglutination after leaving the circulation. There appears to be a reversible and an irreversible agglutination, of which the former is innocuous, or only occurs when the blood is motionless.

An idea seems to have occurred to some minds that the admixture of gum with blood might result in an *increase of viscosity*, and thus tend to overload the heart. This is not the case. I have determined the viscosity of blood mixed with a solution of gum of the same viscosity as itself. The mixture has the same value as either of its constituents.

Chemical Nature.—Gum arabic is a mixture of polymerised anhydrides of galactose (galactanes) and of a pentose sugar, arabinose (arabanes) in varying proportions. The best samples are stated to come from Kordofan and the Blue Nile district. That used in my experiments was in large, clear, nearly colourless lumps, and sold as "Turkey elect." According to the British Pharmacopœia, some samples may contain tannin, which is clearly undesirable. Tests are given in the Pharmacopœia (1914, p. 2), and may be applied easily. No colour should be given with ferric chloride. The "mucilage of acacia" is prepared from tested gum, and may be used for convenience, if appropriately diluted and made 0·9 per cent. in sodium chloride. The dilution required is to add 400 c.c. of water to 100 c.c. of the mucilage. Then add 4·5 grams of sodium chloride to the 500 c.c. But, on the whole, it is simpler to make it from the solid.

In its chemical behaviour it is very inert; like the serum proteins, in fact.

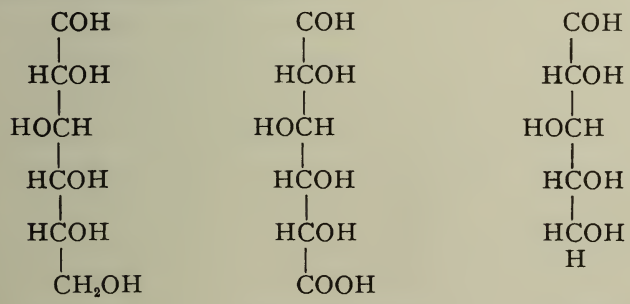
Galactose, as a constituent of milk sugar, is a normal food material and, if the gum is hydrolysed, would be oxidised as a source of energy. As regards arabinose, we shall see that it can be dealt with in animal metabolism, although gum might seem at first sight to be a strange thing to introduce into the blood.

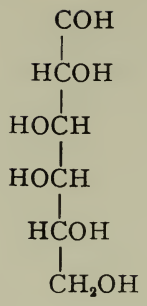
The Fate of Gum in the Organism.—Although it disappears from the circulation sooner or later, it is not yet certain how this takes place. I have found the blood of a cat to give a positive reaction for pentoses twenty-four hours after an injection, but it was absent three weeks later. If it escapes by the urine, it is very slow. I collected the urine of a cat for six hours after an injection, concentrated it to a small volume, but could obtain no pentose reaction. Meek and Gasser (1918), however, obtained it in the urine after large quantities of gum had been injected.

Taken by the mouth, gum arabic is utilised for energy purposes, although not completely (see Magnus-Levy, 1911). If arabinose is given subcutaneously, it is said to be excreted into the intestine. So that it is quite possible that gum or its hydrolytic products may be excreted this way, and if so, they would be utilised as food.

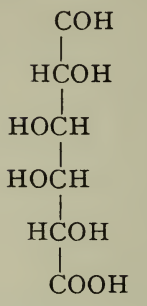
The fact that pentose derivatives can be dealt with by the organism is shown by that curious "error of metabolism" which results in pentosuria (see Garrod, 1909, pp. 136-155). Arabinose is found in the urine in these cases, although this sugar is not known to occur as a constituent of the tissues. It can be shown by feeding experiments

not to come directly from arabanes taken as food. The pentose which enters into the composition of the nucleins of the tissues is xylose, so that the origin of arabinose was for some time a chemical puzzle. It is interesting that a patient is in no way the worse for the existence of pentosuria, so that the metabolic disturbance involved must be a comparatively simple one, and it seems most probable that the explanation given by Neuberg (1904) is the correct one. Glucose, when partially oxidised in the organism, can readily give rise to glucuronic acid. This is not the normal way in which glucose is utilised, but, when the small amount available is used up by conjugation with certain drugs, such as camphor, more is produced. The change of glucose to this acid is by conversion of the terminal CH_2OH group to COOH ; so that it may also be regarded as the carboxylic acid of a five carbon sugar and, if carbon dioxide be removed by the action of bacteria, a pentose is formed. But this pentose turns out to be xylose, the normal constituent of nucleins. On the other hand, suppose we start with galactose and carry it through the corresponding changes, we obtain arabinose. Thus :—

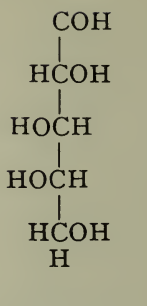




d-galactose



d-galacturonic acid



l-arabinose

Arabinose is thus formed from galactose in the same way as xylose is formed from glucose. Now, all the evidence that we possess shows that the chemical reactions associated with the metabolism of carbohydrates are reversible, with the possible exception of the final oxidative changes. Hence, galactose can presumably be formed from the arabanes of gum as well as from the galactanes present. There are reasons for believing that, in the plant, pentoses are derived secondarily from hexoses (see Cross and Bevan, 1895, p. 185). It is significant that derivatives of galactose and of arabinose are found together in the gums.

Preparation of Solutions.—Commercial gum arabic contains salts of calcium and a small amount of salts of potassium, magnesium, iron, and silicon. It was held at one time that the gum, as found, consisted of salts of an organic acid ("gummic acid") with calcium, etc. Later work indicates that calcium salts, chiefly carbonate, are adsorbed as such. If acted on by hydrochloric acid and precipitated by alcohol, the greater part of the inorganic constituents are still found in the gum thrown down.

There is some evidence, however, of true salts of gum with inorganic bases in the fact which I have met with, namely, that the gum precipitated by alcohol from acid solution, when neutralised by sodium hydroxide, had a higher viscosity than the original one. But this is certainly not a complete proof of the existence of definite salts.

The amount of these inorganic impurities is too small to necessitate their removal. Indeed, they are insufficient to give a 6 per cent. solution of gum in water the requisite saline concentration to avoid breaking up of the blood corpuscles. In reality, they do not seem to count at all, for I found that as much sodium chloride has to be added to a gum solution as to water in order to avoid hæmolysis. The gum, therefore, must be dissolved in 0·9 per cent. sodium chloride. It is unnecessary to add calcium or potassium salts, as the small amounts required are present in the gum already. There is no advantage in adding more sodium chloride than the isotonic amount, nor glucose nor excess of calcium salts, as we have seen.

Unless freshly distilled water is available, it is better to use tap water. The presence of calcium in this latter is only injurious in the case of some special drugs, like salvarsan, where toxic products seem to be formed. Stored distilled water is liable to contain the toxic products of bacteria, even when boiled, and pyrexia has sometimes been known to occur after its use.

In practice it will be found best to dissolve the gum over the water bath. If placed in water and allowed to swell for a day, it dissolves very quickly.

It must be filtered through a rather coarse medium, such as flannel or Chardin paper, to remove bits of wood and so on.

Concentration.—A solution of about 6 to 7 per cent. has the viscosity of blood and the osmotic pressure of the colloids therein. Probably 6 per cent. is strong enough for routine use and has been found experimentally to be quite satisfactory. This strength is now being supplied in the army.

In cases where there is a low blood pressure without evidence of much loss of blood, the 6 per cent. solution may be diluted with 0·9 per cent. salt solution. But, as already remarked (p. 4 above), hasty conclusions must not be drawn from the absence of any great amount of blood on the dressings, etc.

Making the solution hypertonic, as has been done by some, is of no real value and may even be deleterious. The idea was, doubtless, to attract water from the tissues and then to hold it in the circulation by aid of the gum. This result is a very temporary one, because the net effect is the same as if a more dilute gum solution had been used. The preservation of the liquid within the vessels is proportional to the osmotic pressure of the gum.

When gum solutions were first made use of in the treatment of wounded men, the strength was too low, and although Cowell's early results showed much superiority over simple saline solutions, the best possible results were not obtained. In my experiments on cats, 3 per cent. was found ineffective after a loss of 60 per cent. of the total blood, whereas 6 per cent. effected complete restoration. The

comparison was made, of course, by injecting a volume of the gum solution equal to that of the blood removed. A 4 or 5 per cent. solution suffices when comparatively little blood has been lost, but 6 per cent. is always better and may be of value when a weaker solution is not. Rous and Wilson (1918) have found the same facts as myself and they also recommend 6 or 7 per cent. "if one is to bring back the normal pressure in an organism depleted of its fluid reserves."

A large volume of a weak solution, after a brief stay in the vessels, becomes merely equivalent to a smaller volume of a stronger solution. One pint of a 3 per cent. solution becomes half a pint of a 6 per cent. solution, since the water has escaped to the tissues. There appears to have been some fear of overloading the heart by the use of the solutions of a higher viscosity. But if we compare a rise of arterial pressure to the same degree when produced on the one hand by a large volume of a dilute solution, and, on the other, by a small volume of a stronger one, we realise that the work is less in the latter case, because the output of the heart is less. Moreover, there is no reason to suppose that the heart is weak in wound shock, as pointed out above.

THE PRACTICAL USE OF GUM SOLUTIONS

Perfusion of Isolated Organs.

It was shown above that the addition of gum to the Ringer's solution used for such purposes experimentally has the great advantage of avoiding the troublesome œdema that comes on sooner or later.

In some experiments made by Bainbridge and myself, in which the spleen of dogs was perfused for some hours, we found the use of gum solutions of much assistance. Dale and Richards (1918) made use of gum-Ringer for the perfusion of limbs and intestine in their investigation of the action of histamine, etc. The agglutination of cat's corpuscles prevents the addition of blood to gum solutions for such purposes, if accurate records are required of the rate of flow. Otherwise, it is of advantage.

For Intravenous Injection.

Technique.—There is usually no difficulty in introducing into a vein at the elbow a sharp hollow needle of sufficient size to allow the solution to flow

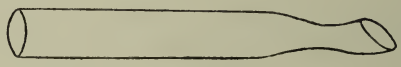


FIG. 30.—**Canula for Insertion into Vein.** Somewhat enlarged.

in at an adequate rate. To facilitate insertion, the vein may be distended by pressing upon it on the heart side of the point where the needle is to be inserted. If the veins are very collapsed, owing to much loss of blood or a low blood pressure, it may be necessary to introduce a canula of glass or metal, after exposing the vein. The ease of introduction depends greatly on the shape of this canula, which should be as in Fig. 30, and need not be large. The method used by Cannon will be found of service. An oblique snip is made into the vein with scissors that must cut up to the points. This incision should cut the vein about half way across. The loose fold

of the wall is then held up with fine pointed forceps, one point of the scissors inserted into the lumen of the vein and a short slit made to continue the oblique incision along that side of the vein towards the operator and parallel to the length of the vein. The opposite wall of the vein then serves as a guide to the canula as it enters. Fig. 31 may explain the procedure, which is simpler to perform than to describe.

The solution must not be allowed to run in at too rapid a rate, otherwise there may be a sudden, but temporary, fall of arterial pressure (see Fig. 32, at *g*). Since the solution contains no oxy-hæmoglobin, the lungs and heart, in turn, are supplied for a brief time with a solution that gives them no oxygen. Although the effect is temporary, it may be alarming. If the fluid is run in by pouring from the bottle of sterilised solution into a funnel attached to the canula by an india-rubber tube, this funnel may be held about two feet above the vein, according to the size of the canula, so as to make the rate of inflow such that one pint flows in during about a quarter of an hour. The bottle may be fitted with two tubes, one passing just through a rubber cork, the other reaching nearly to the bottom. The bottle is then inverted so that the solution runs out of the short tube, while air enters by the long tube. An objection may be made to this method on the ground that, on standing, gum solutions, like most colloids, may form a deposit, which, although it sticks to the bottom of the bottle with some tenacity, may be displaced by inverting the bottle. It would be advisable to tie a bit of flannel over the end of the

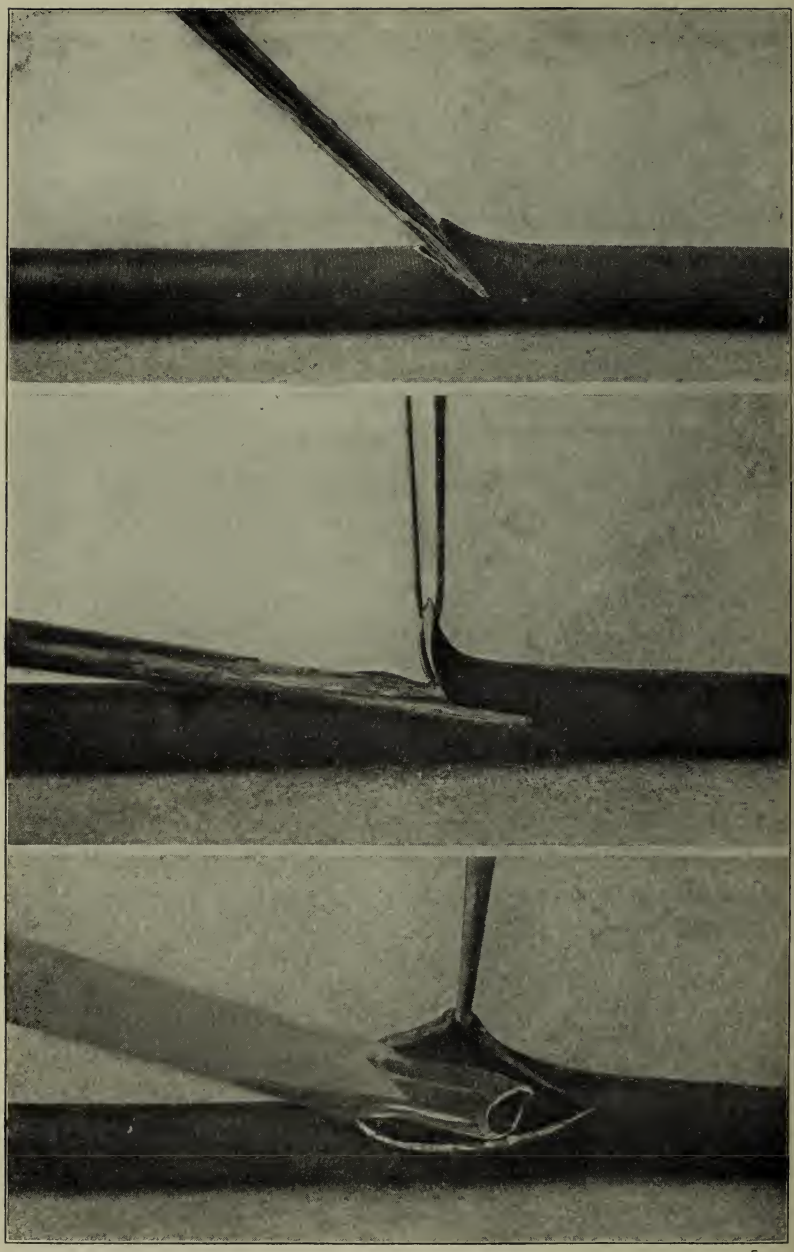


FIG. 31.—**Cannon's Method of Insertion of Canula.**

Illustrated on india-rubber tubing.
Three stages in order from above downwards.

outlet tube, before sterilisation and placing in the neck of the supply bottle. Some users prefer to keep the bottle upright, with the outlet tube reaching nearly to the bottom and having its lower end bent upwards. The solution is then driven out

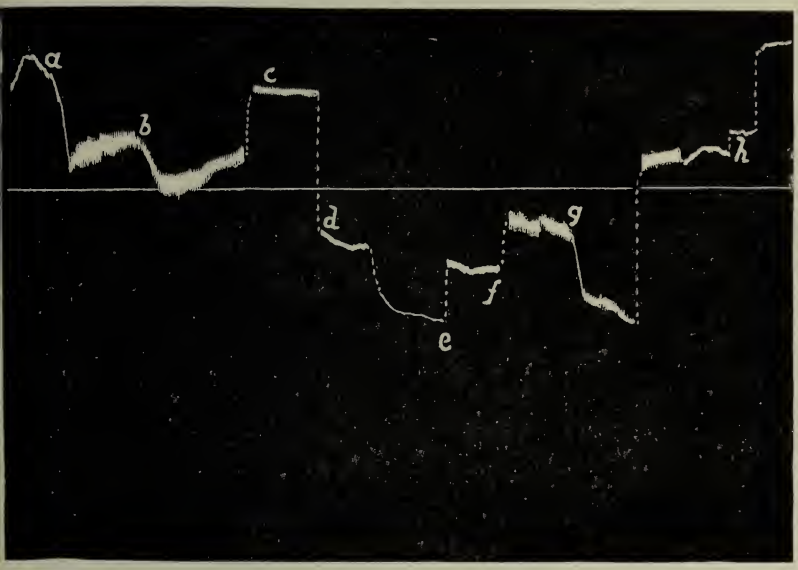


FIG. 32.—**Muscle Injury. Failure of Bicarbonate. Recovery by Gum.**

a. Legs hammered.
b. Massage of legs.
c. After 12 c.c. of 4·2 per cent. bicarbonate.
d. One hour later.
e. 5 c.c. bicarbonate given.
f. 20 c.c. gum-saline given.
g. 24 c.c. gum-saline, run in too fast.
h. Two hours fifteen minutes after gum.
Final height—after section of the vagus nerves.

by pressing a rubber bulb, with valves, attached to the short tube. The outflow can be controlled by

pinching the tube leading to the canula. An outfit with appropriate tubes and canulæ is now being supplied by the Army Medical Department.

Amount to be Given.—Since the amount of blood lost is uncertain, it is best to control the effect of injection by watching the blood pressure. But, if a low pressure has existed long, the vaso-constrictor centre may not recover its full excitability at once, the result being that the arterial pressure continues to rise for some time after the end of the injection. One pint (500 c.c.) may be given as a routine procedure to begin with, allowing fifteen minutes or so for the solution to run in. If the blood pressure does not rise permanently, a second pint may be given half an hour or an hour later. It has been found useful in practice to give a second injection after operation, if there is a low pressure with signs of shock. Drummond and Taylor (1918, p. 6, case No. 2) give a case of wound of the axillary artery, naturally with much loss of blood. The blood pressure was 68 mm. on admission. Transfusion of 550 c.c. of blood raised it to 114 mm. But it had fallen again to 80 mm. by the end of the operation. Gum solution was then given, with a permanent rise to 110 mm., and 130 mm. the next day.

The use of gum solutions in various conditions may now be discussed in more detail.

Hæmorrhage.

This is the simplest case. In Fig. 29 (p. 82) an experiment is given and Fig. 33 gives a further one, in which the gum was not given until four

hours and twenty minutes had elapsed after the removal of 40 per cent. of the blood.

An important point to be remembered is that a prolonged low blood pressure results in a loss of excitability of the bulbar centres. If this has lasted more than a certain time, dependent on the height

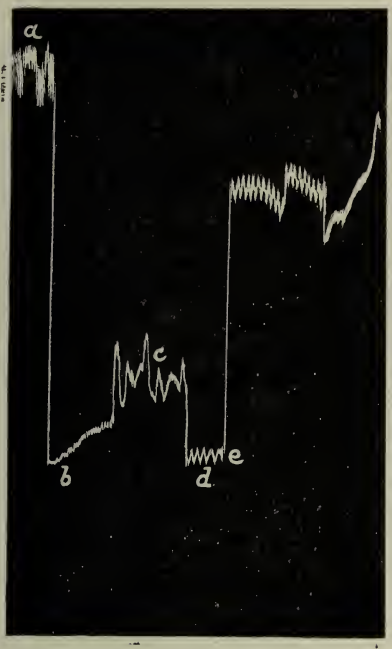


FIG. 33.—**Gum Injection. Four Hours after Hæmorrhage.**

a. Initial height.
b. After removal of 40 per cent. of the blood.
c. 2·5 hours after bleeding.
d. Four hours after bleeding.
e. Blood replaced by 6 per cent. gum, containing 1·8 per cent. of sodium bicarbonate.

End of tracing—three hours after gum injection.

Note.—The blood was of a good arterial colour at *d*. Hence the bad effects of a prolonged low blood pressure appear to be due to insufficient supply, rather than to deficient oxygenation of the blood itself.

of the pressure, no recovery is possible, even by the transfusion of blood. On the other hand, if the paralysis has only recently come on, gum itself may be efficacious, as is found experimentally in cats. It is very probable that, at a certain stage, blood might be effective, when gum is useless. I have some experiments in progress to test this possibility, but have not yet been able to hit upon the right stage. The margin seems to be a narrow one. In the cat the respiratory centre fails first and it is easy to restore the vaso-motor centre at a time when the former centre is beyond recovery. This is in agreement with the results of Stewart, Guthrie, Burns, and Pike (1906) in cases of total anæmia of the brain. In one of my cases the vaso-motor centre failed to respond to stimulation of an afferent nerve after the blood pressure had been for an hour at a level of 50 mm. of mercury. An injection of gum restored it, but the respiratory centre had been paralysed too long and even an hour and a half of artificial respiration, with a good arterial pressure, was ineffective. (See Fig. 34, which is a continuation of Fig. 4.)

Although we have not very exact information on the point, it seems that, in man, the vaso-motor centre may fail before the respiratory centre. The effect of intravenous injection in such cases would not be an immediate or marked rise of the blood pressure, but it would return gradually, as the centres recovered their excitability. For some reason, not quite clear, in the cat without a vaso-motor centre, the spinal animal for example, it is impossible to effect more than a temporary rise of

the arterial pressure even by repeated injections of gum (see Fig. 58 below). The failure is not due to any cardiac factor. The venous pressure does not rise. Blood vessels devoid of central control are able, as it seems, to allow themselves to be distended to a large degree without increase of internal pressure.

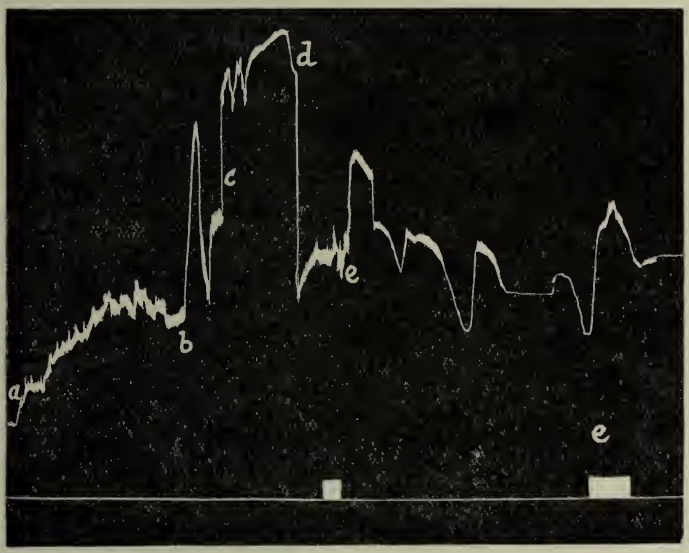


FIG. 34.—**Recovery of Vaso-motor Centre by Gum-Failure to Restore Respiratory Centre.**

Cat under urethane.

a. 25 c.c. gum-saline.
b. 35 c.c. gum-saline.
c. Artificial respiration.
d. Artificial respiration stopped thirty-seven minutes later.
e. Stimulation of sciatic nerve.

Before final tracing, artificial respiration for three-quarters of an hour. On cessation respiratory gasps at the rate of three per minute. Blood very dark.

It appears to me that the practical conclusion to be drawn from the facts concerning paralysis of

nerve centres is that the earlier the intravenous injections are performed, the better. This conclusion was impressed upon me in letters received last year from the front, especially from Lieut.-Colonel Fiaschi, of the Australian Army, and from Captain Bullock, R.A.M.C., who pointed out, as the result of their experience, that the lives of many wounded men might be saved by the use of an appropriate solution at the Advanced Dressing Stations. This is now generally recognised, and arrangements are made for the supply of gum solutions to the forward areas.

An incidental advantage of gum solutions over blood is suggested by the remarks of Captain Oswald Robertson (1918, p. 35). After recommending that cases should be allowed a certain time to recover, if possible, by warmth and rest, he says: "While it may be true that certain cases were passed over in this way who might have been saved if transfused earlier, yet by this procedure it was possible to concentrate a necessarily limited amount of time, energy, and blood on cases reasonably certain to be benefited, and to avoid wasting a considerable amount of blood both on hopeless cases and on those who would recover without transfusion." I feel convinced that any delay is dangerous, and it can rarely be known what cases are really hopeless. Gum solutions ought to be available in large quantity, and no harm is done by their use even when not really necessary. If no benefit results, then recourse should be had to blood, a smaller amount being required than if used alone. Indeed, if there is any advantage in blood, it would seem more reasonable

to reserve it for the more serious cases, which might have gone too far or lost too much blood to react to gum alone, but might be saved by blood. I have no doubt whatever that no hesitation will be felt in agreeing with me that, in so serious a matter as that of life and death, there will be no desire to set up a rivalry between the claims of the two methods. If blood is available in sufficient quantities, and time and assistance are not wanting, use it by all means. But the operation is necessarily more difficult and lengthy, although the use of preserved corpuscles reduces these factors to a large degree. It will be clear that the early use of any method suffers from the disadvantage of giving little information as to its merits, since recovery might have occurred without its use. But this would naturally be no objection when life may be saved. There will, unfortunately, be too many opportunities of testing gum solutions on cases about which there is no question.

Two or three actual cases may be given on account of their instructiveness as to the practical use of gum solutions :—

Drummond and Taylor (1918, p. 5) report the following case : The patient was very pale and restless on admission, no pulse to be felt. Both legs had been severely shattered by a rifle grenade, the right leg blown off. Signs of severe hæmorrhage. Gum solution raised the blood pressure from 76 mm. to 122 mm. Double amputation was performed and the patient made a good recovery.

Another case is reported by Fraser and Cowell (1917, p. 22) and is that of which Fig. 28 gives

a record. It was a case of abdominal wound with severe hæmorrhage and shock. Moribund, blood pressure, 45 mm. At operation, found two pints of blood in peritoneal cavity and six perforations of intestine. Thirty ounces of gum-saline during operation. Fair pulse at end and blood pressure, 80 mm. Next day, blood pressure, 120 mm. Recovery.

Some cases reported by Drummond and Taylor (1918, Nos. 2, 3, and 6) as having much hæmorrhage, but little "shock," are of interest. The latter statement, I take it, means that, although the blood pressure was low, marked signs of collapse had not yet come on. This comparative absence of shock may possibly be connected with the fact that there were no massive injuries to muscular tissue. The significance of this will be seen later.

No. 2. Wound of axillary artery. Blood pressure, 68 mm. Raised to 114 by transfusion of blood. At the end of operation had fallen again to 80 mm. Raised to 110 by gum. Recovery.

No. 3. Injuries to pleura and spleen. Blood pressure, 60 mm. after operation. Gum raised it to 118. Recovery.

No. 6. Wound of kidney. Blood pressure, 60 mm. after operation. Raised by gum to 120 mm. But died three days later from broncho-pneumonia.

Low Blood Pressure from other Causes.

Exæmia is the name suggested by Cannon (1917, p. 81) for that state in which it is clear by the symptoms that there is a deficiency of blood in circulation, although, so far as can be made out,

there has not been much blood lost by actual escape from the blood vessels. In other words, it is possible to have a state of secondary shock without much hæmorrhage.

The blood, or a great part of it, is out of currency. But where is it held up? We have already seen that there is no evidence of its accumulation in large arteries or veins, so that the capillary region is indicated. Cannon, Fraser, and Hooper (1917) find that there is, in wound shock, an increased number of corpuscles in blood obtained from the capillaries as compared with that of the veins. The difference is very small in normal individuals, about 3 per cent.; but in shock it may amount to 33 per cent. The facts referred to above (p. 54) strongly suggest that the capillaries are capable of being altered in volume independently of the arterioles. Dale and Richards (1918) obtain a dilatation of the capillaries with histamine, which constricts the arterioles. Acetyl-choline, on the other hand, dilates the arterioles, but not the capillaries, so far as can be made out.

A low blood pressure tends to excite the vaso-constrictor centre and thus to constrict the arterioles. Usually this is a beneficent reaction to keep up the blood pressure; but, if combined with a commencing stasis in the capillaries, a vicious circle is set up. The reduction of the driving pressure in the beginning of the capillary area allows the blood to accumulate more and more.

However this may be, practical experience shows that the blood which has gone out of currency may be replaced by gum solution, restoring the normal

blood pressure until recovery has taken place and the stagnant blood returned to use. I may refer to three cases of wound shock reported by Drummond and Taylor (1918, Nos. 28, 30, and 32) as suffering from severe shock, but slight hæmorrhage.

No. 28. Compound fracture of both legs. Shell wound of arm. Blood pressure, 76 mm. Gum given during operation raised the pressure to 100 mm. A further injection afterwards raised it permanently to 111. Recovery.

No. 30. Compound fracture of femur. Shell wounds left arm and left foot. Blood pressure, 45 mm. Raised to 110 mm. by gum solution before operation. Maintained for eighteen hours, but died from gas gangrene two days later.

No. 32. Compound fracture of femur. Shell wounds of both arms, ankle-joints, neck, and shoulder. Blood pressure, 74 mm. Raised to 90 mm. by gum solution before operation, and rose further during operation to 116 mm. Recovery.

Remarks on Wound Shock.

At this point attention may be called to the fact that the state called by this name appears to be, as a general rule, the result of a combination of several factors, each alone not being necessarily serious. This view is confirmed by experimental work. Thus, it is found that the removal of one-quarter of the blood from a cat is very rarely followed by any dangerous consequences. But, when a loss of blood is combined with other factors, themselves also attended by some degree of fall of blood pressure, such as cold or injury, a much smaller amount of

hæmorrhage results in a permanent and serious fall of blood pressure, attended by other signs of wound shock. This can, however, be effectively combated by the injection of gum solutions to increase the volume of blood in effective circulation. The practical conclusion to be drawn is that the absence of indications of much hæmorrhage should not be a reason for neglecting intravenous infusion in any case of low pressure. There has been, nearly always, some degree of hæmorrhage, internal or external, in wounded men ; this makes other factors, not dangerous in themselves, of more importance and to be guarded against as far as possible. The loss of blood may be just that occurrence that turns the scale and, if restored, even by gum, recovery may be often assured.

Some of the contributory causes have been already mentioned, but demand some further details, especially in respect of treatment.

Cold.

This is generally recognised at the front as one of the most important factors in exaggerating wound shock (see Cannon, Fraser, and Cowell, 1917, p. 85). Clearly, the most obvious precaution is to keep the patient as warm as possible. Warmth and water are the most insistent demands of the wounded.

But certain experimental work indicates that, if the body temperature has fallen much, the existence of a small amount of hæmorrhage may prevent recovery on warming up. In wounded men, mouth temperatures of 87° F. have been met with. In experiments made by Cannon and myself, we found

that cats could be cooled to 25° C. rectal temperature and completely recovered by warming (Fig. 35). This was not the case, however, if the cold was

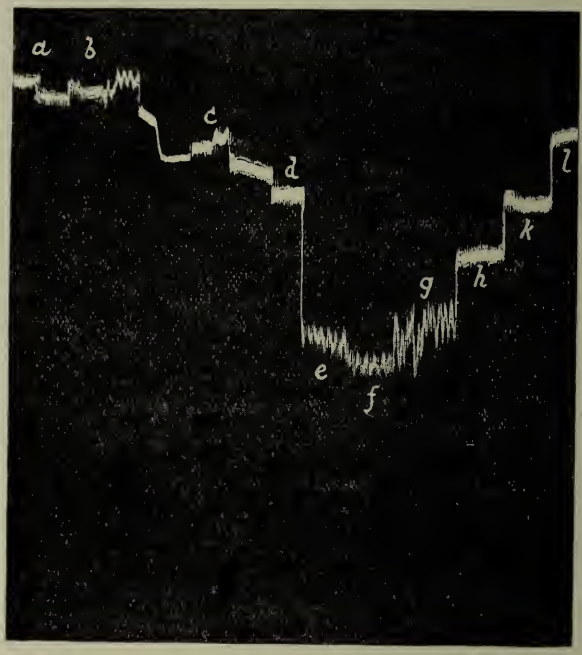


FIG. 35.—**Cooling with Recovery.**

Cat under urethane.

a. Commenced cooling. Temp. 35·8°.
b. Temp. 34°. Shivering.
c. 1·25 hours later. Temp. 30·8°.
d. After another hour. Temp. 28°. Pulse 128. Resp. 32.
e. Forty minutes later. Temp. 25°. Pulse 64. Resp. 10. Apparently heart block. Muscles lax, no shivering.
f. Began to warm.
g. Shivering. Temp. 26°. Pulse 106. Resp. 20.
h. Half-an-hour after *f*. Temp. 27°.
k. Seven minutes later. Temp. 28°. Pulse 130. Resp. 28. General shivering.
l. Seventeen minutes later. Temp. 30°. Pulse 140. Resp. 36.

In a similar experiment on a decerebrate cat, the absence of shivering was notable, but there was increase of rigidity on cooling.

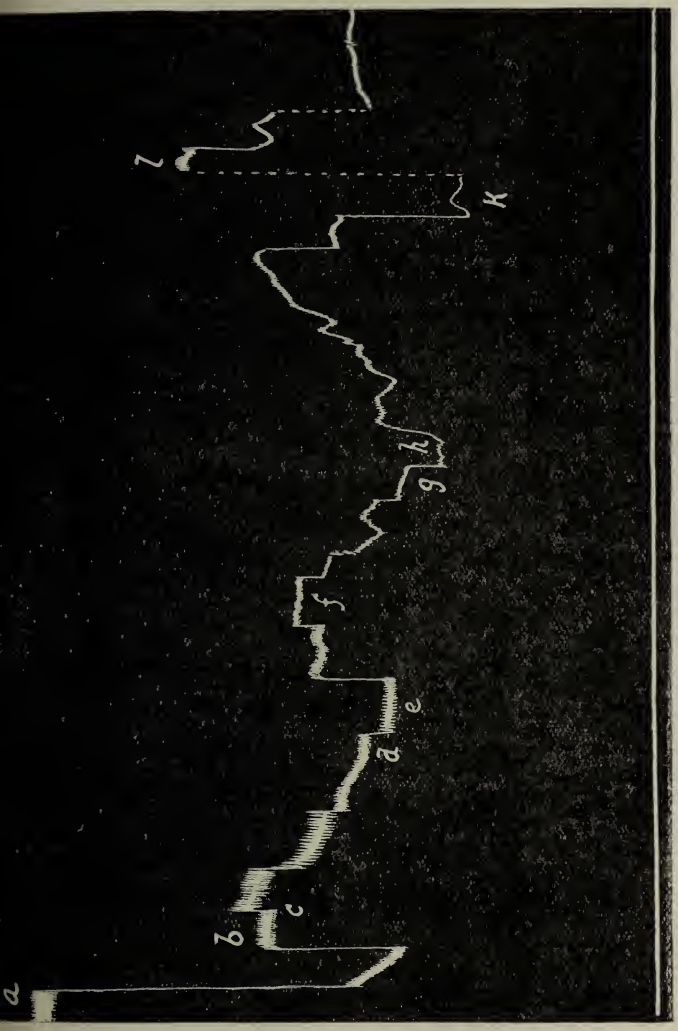


FIG. 36.—Cold Combined with Hæmorrhage. Effects of Bicarbonate and of Gum.

a. Bled 26 per cent.
b. Spontaneous partial recovery of blood pressure.
c. Began to cool.
d. Temp. 30·8°. One hour later.
e. Temp. 27°. Began warming.
f. Temp. 28°. Fifty minutes after *e*.
g. Temp. 33·5°. One hour forty-five minutes after *f*.
h. One hour later. Ten c.c. of 8 per cent. bicarbonate.
k. Thirty-six minutes later. 50 c.c. of gum-saline given.
l. Half an hour later.
Final level—one hour after gum.

combined with a loss of blood of 23 to 30 per cent. (See Fig. 36.)

The effect of cooling is to lower the blood pressure, chiefly by slowing of the heart beat. But

there must be some additional factor after slight hæmorrhage, because the pressure does not recover on warming. Recovery may be obtained, however, as I have recently found, by an intravenous injection of gum, not by bicarbonate (Figs. 36 and 37).

Injury to Muscular Tissue.

I propose to discuss this cause of wound shock in some detail, because it appears to be that form of experimental shock most nearly akin to that of wounded men, especially when accompanied by slight hæmorrhage.

Surgeon-General Cuthbert Wallace, in a letter to the Committee on Shock, remarks on the great liability to shock after operations in which large muscular masses were cut. He says: "In amputations of the lower limb, shock increases as the body is approached. On the other hand, an interscapular thoracic amputation is not accompanied by much shock. The actual size of the wound in the latter is not far removed from that in amputation at the hip joint." "The difference consists in the amount of muscle cut through, and in the amount lost to the body." That the latter is not a great factor is indicated by this fact: "In tuberculous disease of the hip, the limb is removed in the middle third on one day, and the top of the femur taken out after a few days. The second stage is the dangerous one. The amount of muscle cut through is much greater in the second than in the first stage." "Comparing upper and lower limb amputations and the two stages of the lower limb amputation, it

would seem that muscle section is a factor in producing shock."

The experience of the present war confirms this view in many respects. The especial liability of compound fractures of the thigh and of multiple wounds to shock has been noticed, although it must

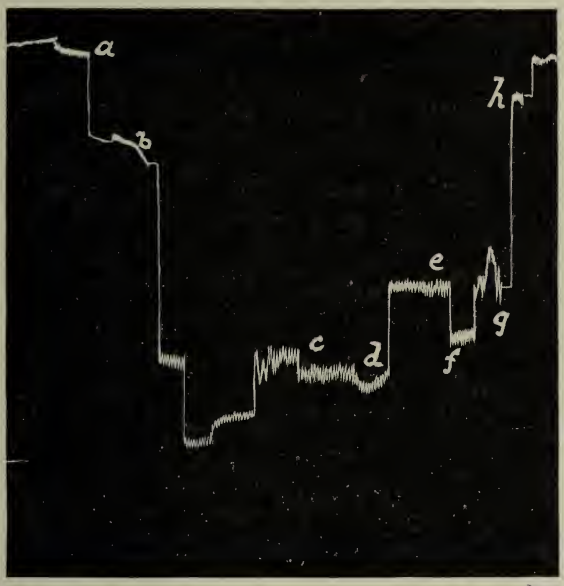


FIG. 37.—**Hæmorrhage Followed by Cold. Effect of Gum.**

a. Bled 30 per cent.
b. Began to cool.
c. Temp. 29° C. (84° F.). Began to warm.
d. Gum, 32 c.c.
e. Temp. 29·2°.
f. Fifty minutes after *c.* 12 c.c. gum.
g. Temp. 29·8°. Eighteen minutes later.
h. Two and a half hours after *g.* Temp. 33°.
Final height at one hour eight minutes after *h.* Temp. 33·6°.

not be supposed that it is only injuries to muscle that result in shock. It may have been observed

that the cases reported on p. 104 above as of severe shock were all of extensive muscle injuries. The following case, given by Cowell (1917, p. 65), is instructive: A man was brought to the Advanced Dressing Station within fifty minutes of receipt of shell wounds. He was found to have severe multiple wounds, including compound fractures of femur and humerus with laceration of the muscles, which looked like dead tissues. There was no bleeding and very little capillary oozing, but the blood pressure was only 40 mm. of mercury. Mentally, he was quite bright. He died, nevertheless, within an hour. It is interesting to note that the low blood pressure had not existed long enough to affect the nerve centres at the time of admission.

Before passing on, a word may be said with respect to *fat embolism*. This has been met with in fractures of long bones, but there is little or no evidence that it plays any important part in the phenomena with which we are now dealing. In the experiments to be described below, no difference was noted in the result whether the femur was broken or not and no sign of fat emboli was observed, post mortem, in the lungs. The operation for tubercular hip joint described above by General Cuthbert Wallace shows that the dangerous stage is not that when the femur is sawn through.

The state of wound shock can be imitated in many respects by crushing and laceration of the thigh muscles in anæsthetised cats, as was found by Major Cannon and myself. This work has recently been extended somewhat by me, but further investigation is still required. The injury was usually

made by hammering the flexor muscles of both thighs against an iron block. The hammer weighed about one pound. The skin was not usually broken. Sometimes the femur was broken, sometimes not. When examined post mortem, the state of the muscles reminded us very strongly of the shell

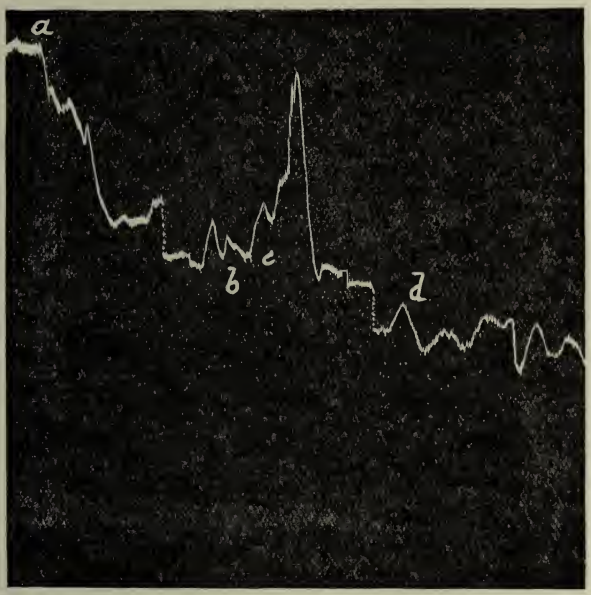


FIG. 38.—**Muscle Injury. Spinal Cord Cut.**

Cat under urethane. Cord cut in upper lumbar region.

a. Hammered legs. No bone broken.

b. Respirations, 120 per minute.

c. Temporary occlusion of trachea to test excitability of vaso-motor centre. One hour and ten minutes after injury.

d. Two hours after injury. Resp. 156.

End—two and a half hours after injury.

Bicarbonate reserve—Before injury	42
At *c*	42
At *d*	37
At end	31

wounds which we had seen in France. There was a destruction of the tissues, but not a very great extravasation of blood. Notwithstanding this last fact, the legs swelled greatly, apparently due mainly to escape of liquid from the blood, since hæmatocrite

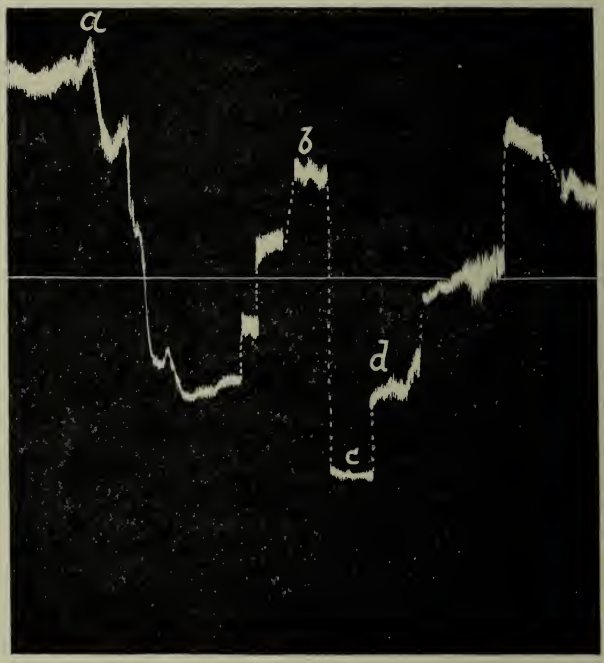


FIG. 39.—**Muscle Injury. Recovery. Hæmorrhage. Gum.**

Cat, 2·8 kilos.

a. Hammered legs.

b. Spontaneous partial recovery, fifty minutes later.

c. After removing 24 per cent. of the blood.

d. Sixteen minutes later. Resp. 130, shallow. Fifty c.c. gum solution given. Reduced respirations to 22, blood pressure rose to 136 mm. in a quarter of an hour.

Last level—two and a half hours after gum, three and a half hours after injury.

estimations showed a progressive concentration of the blood.

During the infliction of the injury, the blood pressure falls, sometimes very notably, as in Fig. 38. If the fall is not very great, partial spontaneous recovery may take place, as in Fig. 39; but the

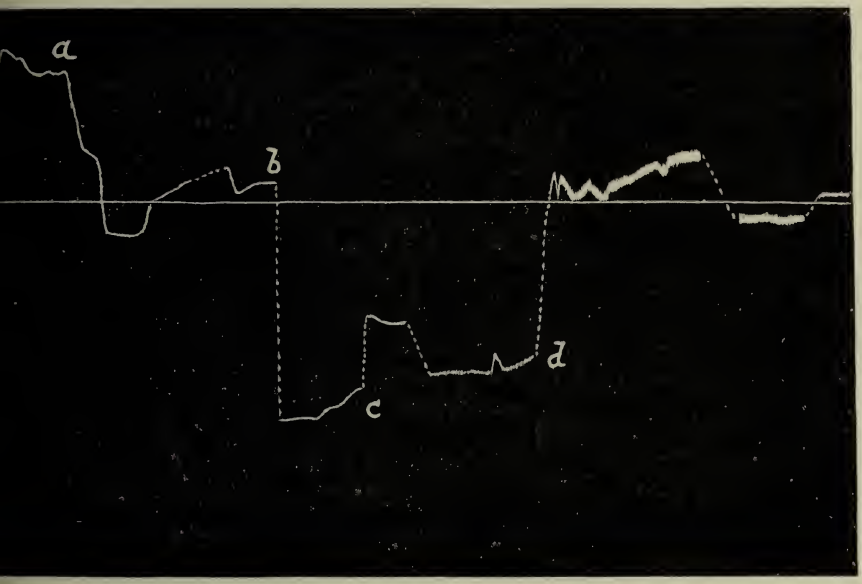


FIG. 40.—**Muscle Injury. Shock Exaggerated by Hæmorrhage. Effect of Gum.**

a. Legs hammered.
b. Bled 22 per cent., fifteen minutes later.
c. Gum-saline, 28 c.c.
d. ,, 13 c.c.

End of trace—two and a half hours after gum, three hours after injury.

primary fall is usually followed by a slow secondary fall, ending in death, as in Fig. 38. In either case, a slight hæmorrhage, even of 22 per cent., has the

effect of enormously exaggerating the state of shock, as seen in Fig. 40, or of bringing on the secondary shock, as in Fig. 39. A loss of this amount of blood is quite innocuous to the normal cat.

The blood pressure can, however, even after exaggeration by hæmorrhage, be restored by the injection of gum-saline, as shown by Figs. 39 and

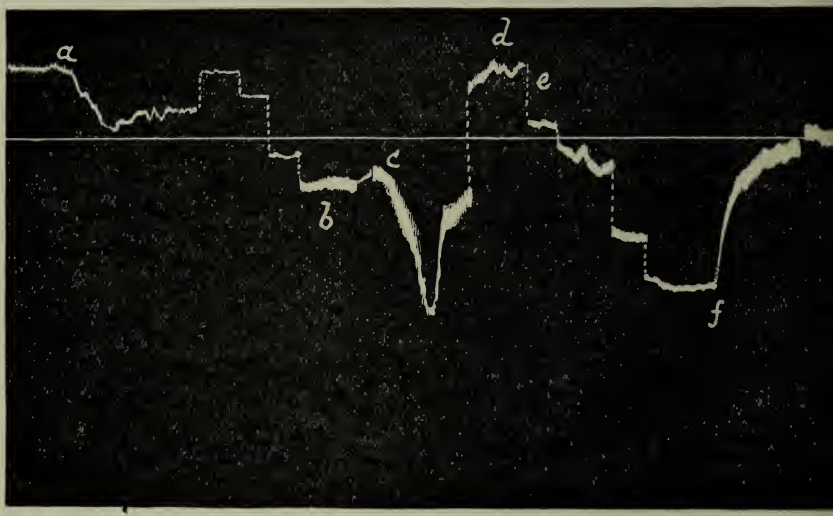


FIG. 41.—**Muscle Injury. Lactic Acid. Gum at Late Stage.**

a. Legs hammered. Severe injury, although not much immediate fall of blood pressure. Resp. 30.
b. Two hours after injury. Resp. 56, irregular.
c. An hour and a quarter later. Injection of 13·5 c.c. of half normal lactic acid. Fall due to rapid injection.
d. Two hours later. Complete recovery.
e. Rebreathing (92 cm. tube) for half an hour.
f. Gum-saline, 28 c.c. Five and a half hours after injury.

Last tracing—forty-one minutes later.

40; while Fig. 41 shows that a good result can be obtained five and a half hours after injury. If gum

be given in small amounts at intervals, as the blood pressure shows signs of falling, shock can be avoided, even after extremely severe injury (Fig. 42).

There is usually some degree of concentration of the blood in the early stages after the muscle injury, notwithstanding the fall of blood pressure, which would itself cause a dilution. In the later stages, this concentration disappears, probably becoming obscured by the effect of the low pressure. The concentration taking place, although, experimentally, not great, might suggest that the viscosity of a 6 per cent. solution of gum might be too high. In wounded men, however, there has nearly always been more or less loss of blood, and this strength of gum has shown itself so much superior to weaker solutions that I have no hesitation in recommending its use invariably. In point of fact, there is no evidence that the heart has become weak in wound shock. In laboratory experiments, it is able to keep up a high pressure after gum has been injected, and the results of Markwalder and Starling (1913) showed that, after a period of low pressure, the heart returns to its original strength of beat on raising the pressure.

The cause of the fall of blood pressure after muscle injury is evidently the passage into the blood of some chemical products of the destroyed tissue. That a nervous reflex is not the responsible factor is easily shown by dividing the spinal cord in the upper lumbar region before the injury to the muscles. In Figs. 5, 38, and 43 *B*, this had been done. Further, if the iliac arteries and veins be clamped during the infliction of the lesion, no fall of

blood pressure occurs until the clamp is removed, although the nervous connections are intact (see Fig. 46 below).

In the light of the experiments of Fletcher and Hopkins on the production of lactic acid in excised muscles when they are crushed, it might be thought that "acidosis" of this origin might be responsible

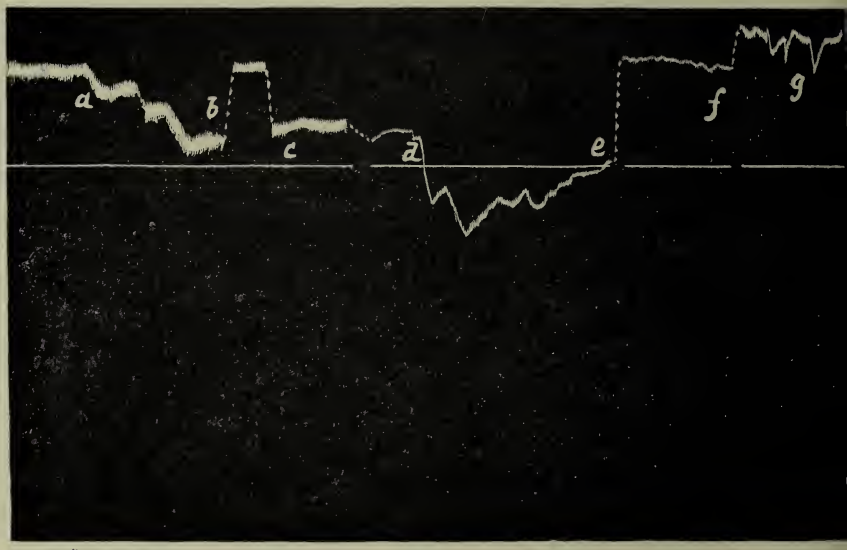


FIG. 42.—**Severe Muscle Injury. Massage of Muscles. Gum at Intervals.**

a. Hammered legs. Much swelling and extravasation.
b. 20 c.c. gum.
c. 15 c.c. gum.
d. Massage of legs.
e. 15 c.c. gum.
f. 4 c.c. normal lactic acid and 4 c.c. gum.
g. Four and a half hours after injury.

for the primary fall. But the bicarbonate reserve does not decrease, so that some other chemical

substance must be looked for. There is, on the other hand, as a rule, a diminution of the bicarbonate in the secondary fall. This might be, and probably is, the result of the low blood pressure, rather than its cause. Araki (1891) showed that a low blood pressure causes the production of lactic acid in the tissues. Moreover, recent experiments have shown

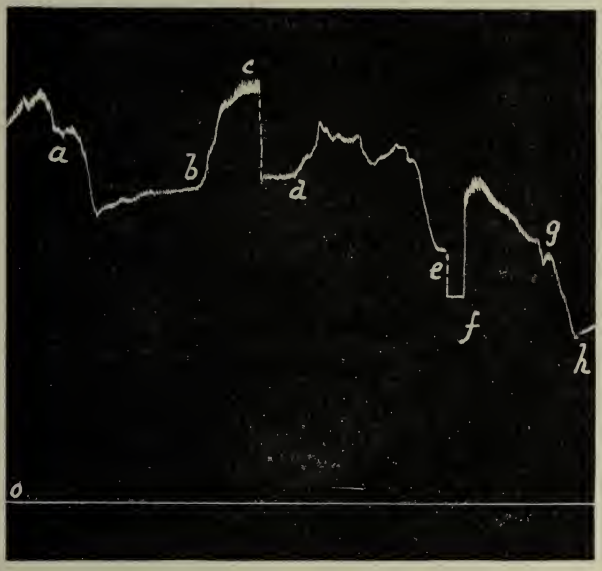


FIG. 43.—*A*.

Failure of Bicarbonate after Muscle Injury.

Experiment similar to that of Fig. 42.

a. Hammered legs.
b. 25 c.c. of 4·2 per cent. bicarbonate.
c. Hammered right leg again as the previous injury had been slight. No bone broken.
d. 15 c.c. bicarbonate.
e. An hour and a half after injury.
f. 5 c.c. bicarbonate.
g. Attacks of respiratory gasps, followed by very shallow respiration.
h. Two hours after injury.

me that lactic acid is innocuous in wound shock (see Figs. 41 and 42). The injection of sodium bicarbonate does not prevent the development of shock after muscle injury (Figs. 32, 43, and 45); whereas that of gum-saline does (see Figs. 32, 40, 41, and 42).

A further test was made by extracting muscles, which had gone into rigor, with boiling saline solution. A part of the extract was neutralised.

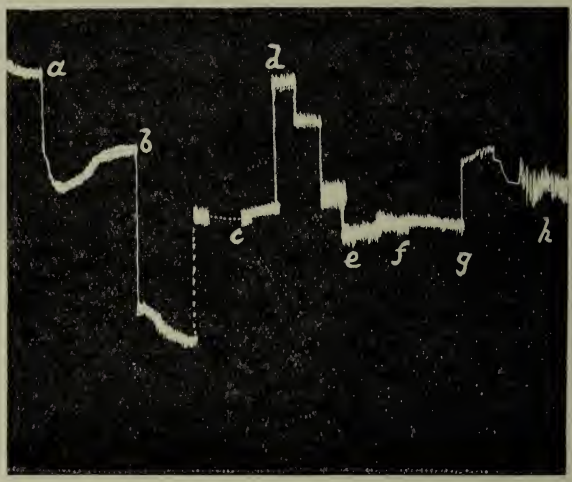


FIG. 43.—*B*.

Failure of Bicarbonate after Muscle Injury.

Cord cut in upper lumbar region. Hæmorrhage.

a. Legs hammered. Resp. 80.

b. Bled 27 per cent.

c. Partial recovery, but respirations rapid, about 82, with gasps at intervals.

d. After 50 c.c. gum-saline. Resp. 36.

e. One hour and ten minutes later. Probably gum insufficient in amount. Respiration rather sighing.

f. 15 c.c. half-normal bicarbonate.

g. Twenty minutes later, 15 c.c. gum.

h. Half an hour later.

In this experiment gum had only a temporary effect, although it was better than bicarbonate.

The effects on the blood pressure and on the intestinal vessels produced by equal doses were the same. Hence the vaso-dilator substance is not lactic acid (Fig. 44).

FIG. 44.—**Effects of Extract of Muscle.**

Upper tracing—volume of intestine in plethysmograph.

Lower tracing — blood pressure. Line at bottom—zero of blood pressure.

a. Neutralised extract, 5 c.c. into vein.

b. Unneutralised (acid) extract, 5 c.c.

Vincent and Sheen (1903) have described similar vaso-dilator effects from muscle extracts. According to Sand (1917), toxic products are formed by the disintegration of injured muscles, whether produced by the direct mechanical effect of shell fragments, or by gas infection. Dale and Richards (1918) show that histamine dilates the capillaries and suggest that substances similar in action to it are produced by injury to tissues. The result of a widespread dilatation of capillaries would be a draining of large amounts of blood into them and its loss to the currency, equivalent to a hæmorrhage, as pointed out above. Dale and Laidlaw (1917) have observed a state of shock after somewhat large doses of histamine, and it would be

of interest to know what effect the injection of gum solution has upon the low blood pressure produced in this way (see below, p. 141).

It has been already mentioned that, if the abdominal aorta and the vena cava are clamped during the injury to the muscles, the fall of blood pressure does not come on until the clamp is removed. Fig. 45 is an experiment of this kind. The time that elapsed from the closing of the clips until they were reopened was less than four minutes, and during this time the legs were hammered. It will be noticed that the blood pressure recovered after a time, and then the legs were hammered again, with a progressive fall of blood pressure as the result. An injection of sodium bicarbonate caused merely a temporary rise of pressure.

It seems probable that the first rapid fall of blood pressure may be partially due to the emptying of blood into the dilated vessels of the injured area, and, to some extent, to the hæmorrhage into the damaged tissues. The latter factor is not usually great in experiments of the kind described. In actual shell wounds it is naturally of a very variable degree. The experimental shock is occasionally rather slight and spontaneously disappears. It may be suggested that, if the blood vessels become more or less impervious by the formation of clots or pressure upon them, the toxic products will not have a free outlet into the circulation.

Whatever these dilator substances may be, they appear to be removed by oxidation, like lactic acid is. The fact is shown by the rapid disappearance of the effect of a small dose, as in Fig. 44. The

practical conclusion to be drawn is the importance of improving the supply of oxygen by raising the blood pressure.

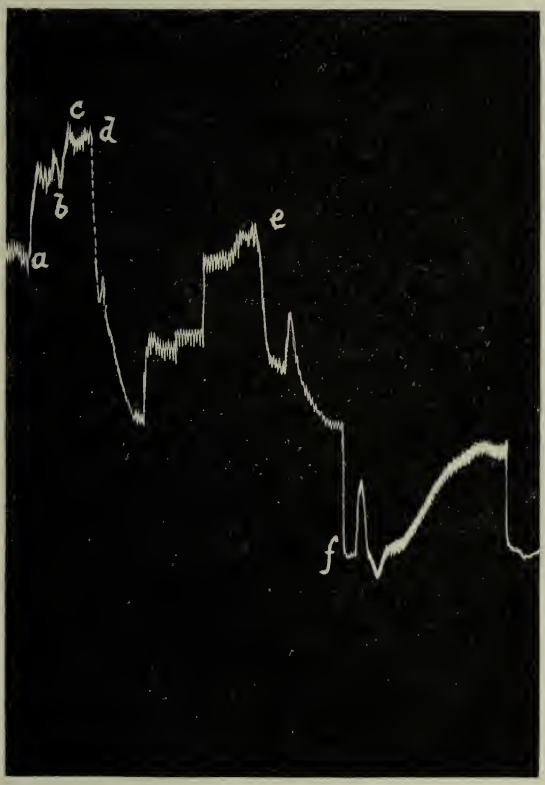


FIG. 45.—**Muscle Injury with Vessels Clamped.**

a. Clip placed on aorta above iliac arteries.
b. Clip on vena cava.
c. Legs hammered.
d. Both clips off.
e. Partial recovery in half an hour.
f. Legs hammered again.
g. An hour and a quarter later. 10 c.c. of 5 per cent. bicarbonate given.

End of trace—forty minutes after *g*.

Massage of the injured muscle has the effect of causing an increased fall of blood pressure (see Figs. 42 and 46), doubtless by augmenting the flow of the toxic products into the general circulation. This fact serves as the experimental justification for the use of the Thomas splint, which has been found so beneficial in the transport of cases of fractured femur (see Cowell, 1917, p. 61), preventing the injured parts from moving (see also Charles, 1918). The incidence of secondary shock is said to have been greatly diminished by its use.

FIG. 46.—Vaso-dilator Effect of Massage of Injured Muscle.

Upper tracing—intestinal plethysmograph.

Lower tracing — blood pressure. Horizontal line—100 mm. pressure.

At *a*, massage of legs. The lever of the recorder was lowered by letting out air at *b* and at *c*.

McNee's experience of a large number of cases of wound shock has convinced him that the absorption of toxic products from injured muscle is one of the most potent causes of the condition. He has observed that the removal of the disintegrating tissue, as by amputation of the limb, is rapidly followed by a great improvement in the state of the patient. Even the application of a tourniquet to prevent

the passage of the deleterious substances into the circulation is of much value. He has also been able to exclude definitely the participation of bacterial infection in the phenomena. Keith (1918) found in such cases, by the use of the vital red method, a diminution in the volume of the blood in circulation; a further indication for introduction of fluid and a confirmation of the view that stasis in capillary areas plays an important part in wound shock.

There is an interesting respiratory effect in experimental shock by muscle injury, to which reference has been made above (pp. 16 and 46). A very rapid, shallow respiration is nearly always present. At the point marked *b* on Fig. 47 the respiration was 180, the pulse 186.

This is also a common symptom in wound shock in man. So far as we can tell at present, it appears to be a form of the exaggerated Hering-Breuer reflex, described by Haldane, and due, in this case, to an increased sensibility of the respiratory centre to the inhibitory impulses set up in the vagus by the inspiratory stretching of the lungs. If the vagi are cut before injuring the muscles, the effect is absent. It would, perhaps, be more convincing to be able to abolish it by cutting the vagi after the injury, and experiments of this nature are in progress. The increased excitability of the respiratory centre seems to be a stage in its failure from deficient supply of blood. At all events, as Fig. 5 shows, normal respiration is restored by the injection of gum-saline. The type of respiration in question is also produced by loss of blood, but is then usually transitory, being

followed quickly by a *slow*, shallow type, owing to the centre failing rapidly in the cat (see Fig. 11). In very severe cases of wound shock, such as terminate fatally whatever is done, McNee (1918) has noticed that the respiration is not quickened

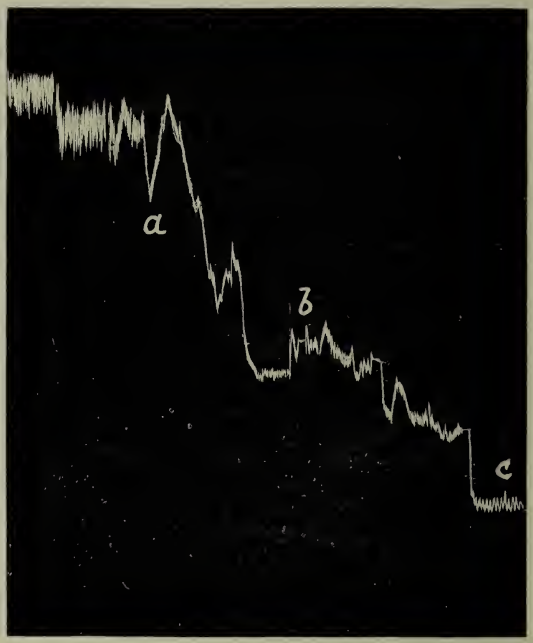


FIG. 47.—**Muscle Injury with Very Rapid Respiration.**

a. Legs hammered (femur broken).
b. One hour afterwards. Resp. 180. Pulse 186.
c. Half an hour later. Artificial respiration necessary.

Bicarbonate reserve—Initial	46
Half an hour after injury	47
At *b*	41
At *c*	34

and appears fairly normal. There is no evidence of hyperpnœa, a fact which excludes acidosis as an

important factor. Moreover, the injection of bicarbonate is of no benefit. It seems probable that the nerve centres are on the way to paralysis, and indeed Mott (1918) has detected changes in the nerve cells in such cases. The state may be comparable to the second stage in the cat, as described above. Mott states that the chromatolytic changes are identical with those found in prolonged experimental anæmia of the brain.

Effect of Anæsthetics.—It has been the general experience that there is danger of an operation exaggerating the state of shock. It seems likely that this may be due to a deficient supply of oxygen to the tissues, caused by the action of the anæsthetic on the respiratory centre, which adds itself to the effect of the low blood pressure already present. In experiments on animals, one usually has opportunity of observing the colour of the arterial blood and I have found it a matter of some difficulty to maintain anæsthesia with ether without the blood becoming more or less venous in colour. Cannon (1917, p. 53) obtained evidence of increased production of acid in the tissues under ether, sometimes even under nitrous oxide and oxygen. But this does not occur if an adequate supply of oxygen is ensured, as is possible under the latter form of anæsthesia. Marshall (see Cannon, 1917, p. 69), as the result of a large experience at a Casualty Clearing Station, states that "if a patient becomes cyanosed, he loses ground which can hardly be recovered." For this reason, he advocates nitrous oxide and oxygen as the proper anæsthetic to use in cases of shock.

Ether readily produces a fall of blood pressure after the "alkaline reserve" has been decreased by injection of acid or by want of oxygen. Fig. 48 serves to illustrate this fact, which has been noticed by Cannon, by Dale, and by myself, but is not yet explained.

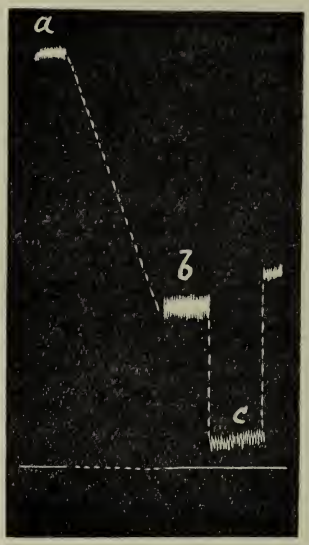


FIG. 48.—Effect of Ether after Acid.

a. Height of blood pressure under ether.

b. Height after acid injection, combined with 26 per cent. loss of blood and replacement by gum. Ether decreased, owing to failure of respiration.

c. Fall of blood pressure with ether at its original amount.

Horizontal line at 100 mm. pressure.

Since it is scarcely possible to avoid some fall of blood pressure in operations, there may be risk when the blood pressure is already low. For this reason, it has been found of benefit to raise the pressure before or during the operation by the injection of gum-saline. Three cases reported by Drummond and Taylor (1918, Nos. 18, 19, and 24, p. 8) are to the point. In No. 18 there were shell wounds of abdomen, knee-joint, leg, and wrist-joint. Blood pressure on admission, 135 mm. Fell to 80 during operation. Restored to 104 mm. by injection of gum, and maintained. In No. 19, although the blood pressure was 120 on admission, it fell to 80 by the end of the operation. Gum-saline was given, the blood pressure was restored to 118 and remained

there. In No. 24, a case of severe multiple wounds, the blood pressure was between 86 and 64 on admission. Gum was given before operation, raising the pressure to 124. A second infusion was given during the operation and, at the end, the pressure was 92 mm., although the patient died twelve hours later.

It is difficult to realise, experimentally, the appropriate conditions; but, in some cases where there was apparently some fall of blood pressure due to the anæsthetic, gum-saline was found to be of benefit. But I would not lay stress on these results.

Asphyxial Conditions.

These are doubtless closely related to the deleterious effect of certain anæsthetics. I wish here to call attention to some results obtained, chiefly in experiments made in conjunction with Major Cannon, on the breathing of air containing excess of carbon dioxide, or deficient in oxygen, or a combination of both.

The effect of carbon dioxide itself in excess is double. It is well known that the first effect is a rise of blood pressure owing to stimulation of the vaso-constrictor centre. If continued, a pronounced fall of pressure follows, as shown in Fig. 27 (p. 73), probably due to a combination of Patterson's effect on the heart with peripheral vaso-dilatation. It is more or less rapidly recovered from when the inhalation ceases, and leaves behind no ill effects. It may, however, be of importance when expired air is rebreathed, as sometimes happens in the administration of ether, and also, if the blood pressure is already low from wound shock.

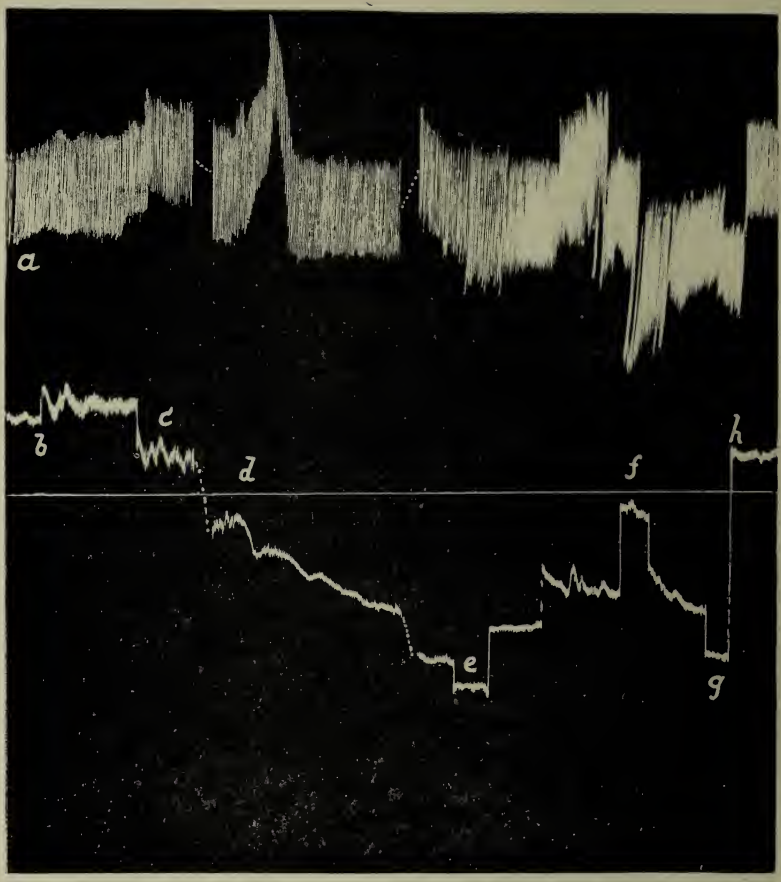


FIG. 50.—**Hæmorrhage and Deficient Oxygen Afterwards.**

19 per cent. of the blood removed first of all. Then short period with 200 cm. tube as in Fig. 49.

a. Normal.
b. Rebreathing, 100 cm. tube.
c. Twenty-eight minutes after *b*.
d. Rebreathing stopped.
e. Thirty-four minutes after *d*.
f. Eighty-four minutes after *d*.
g. Ninety-four minutes after *d*.
h. 111 minutes after *d*.

Note that a much more serious fall of blood pressure occurred than in the preceding figure (70 mm. instead of 18 mm.), and that, although recovery ultimately took place, it was delayed for nearly twice the time. The partial temporary recovery at *f* is interesting, but the rise of blood pressure appeared to be asphyxial.

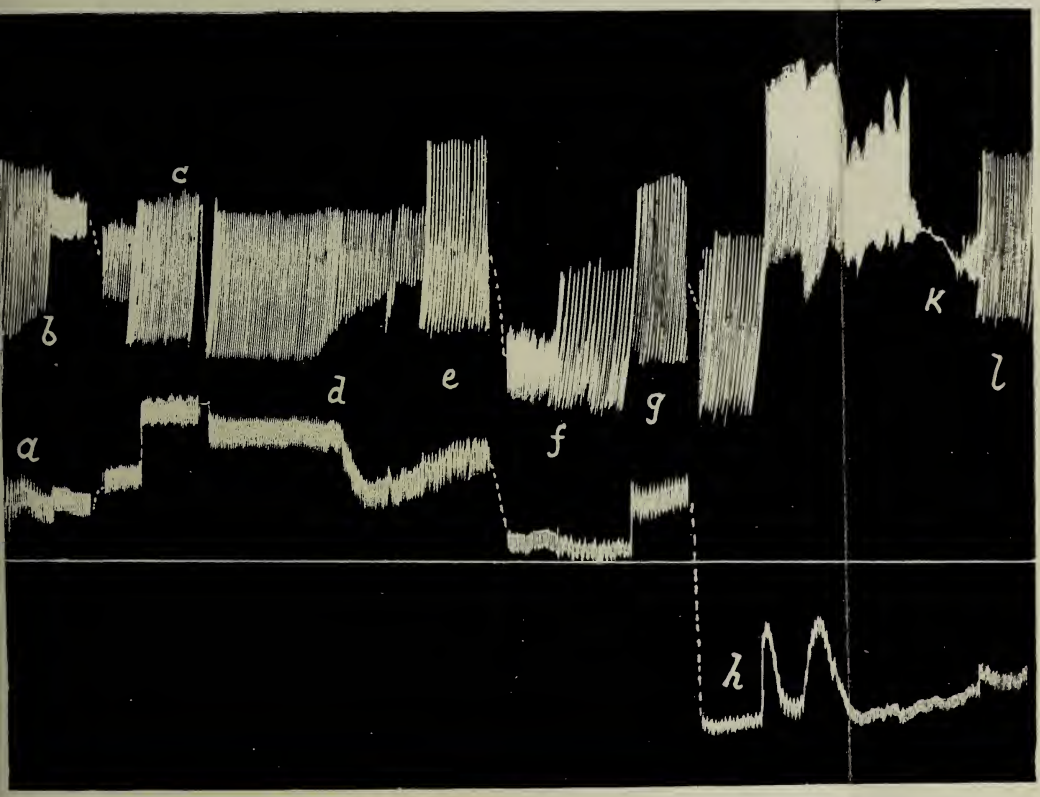


FIG. 49.—**Deficient Oxygen in Respired Air. Hæmorrhage Later.**

Upper tracing—respiration.

Lower tracing—blood pressure. Horizontal line at 100 mm. of mercury. Before the record began, a period of five minutes' rebreathing expired air with carbon dioxide absorbed (tower with continuous dripping of caustic soda, close to trachea), length of tube, 200 cm. altogether. Respiration stopped, but was restored.

a. Normal.

b. Rebreathing commenced, tube 100 cm., CO_2 absorbed as before.

c. Twelve minutes after *b*. Note rise of arterial pressure.

d. Rebreathing ended, after half an hour's duration.

e. Ten minutes later.

Five minutes after *e*, breathing ceased. Artificial respiration for a few minutes.

f. Twenty-one minutes after *d*.

g. Seventy-eight minutes after *d*. *Recovery*.

h. Four minutes after removing 17 per cent. of the blood.

k. Temporary stoppage of respiration, preceded by attack of dyspnœa, half an hour after bleeding.

l. Forty-three minutes after bleeding.

Note that a small hæmorrhage after deficient oxygen produces a long-lasting fall of pressure and disturbance of respiration. A further point of interest is that, although the blood pressure was higher than normal at the end of the period of deficient oxygen supply, it was followed by a depression of long duration and a temporary stoppage of respiration.

[*To face page* 128.

On the other hand, defect of oxygen, even when there is no excess of carbon dioxide, although less obvious in its immediate effects on the blood pressure, is very apt to leave behind a condition in which there is a progressive fall of blood pressure, while the blood becomes more and more venous (see Fig. 49). This is especially the case after a slight loss of blood (Fig. 50). In such cases, the heart seems to recover, but a vicious circle is established as regards the respiratory centre, since defective oxygen supply reduces its excitability and less and less oxygen is taken in by respiration.

It is a matter of some interest that, in cats at least, the vaso-motor centre is more sensitive to low blood pressure than to want of oxygen in the blood. In Fig. 51 we see that the vaso-motor reflex is not abolished when the blood pressure has already fallen very low and the respiration has ceased. The first three-quarters of an hour of deficient oxygen had no effect on the vaso-motor reflex, not much on the respiratory centre, but a permanent effect was left behind, because the centres were more easily affected by later applications of the same deficient supply, even after an hour's interval with not so great a deficiency. The delayed effects of asphyxial conditions due to want of oxygen have an importance in connection with the effects of pulmonary irritant gases and with the possibility of cumulative action in the case of the airman. Investigations are, indeed, being made on these lines.

The *rebreathing of expired air* has been recommended by Townshend Porter and by Yandell

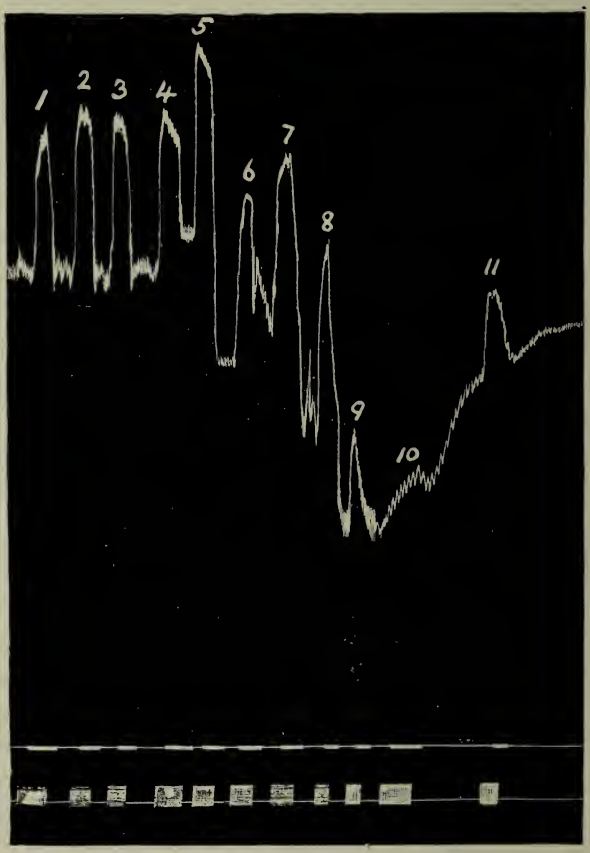


FIG. 51.—**Effect on the Vaso-motor Centre of Breathing Air Deficient in Oxygen.**

First stimulation, of central end of sciatic nerve, ten minutes after commencement of rebreathing expired air with the carbon dioxide absorbed by sodium hydroxide close to the tracheal canula.

After the fourth stimulation, forty minutes after commencement, more oxygen was admitted by the use of a shorter tube, since the respiration began to fail. The long tube was replaced after an hour, but breathing soon stopped, so that it had to be removed. It was replaced again ten minutes later, and six minutes afterwards stimulation 7 was obtained. No. 8 was two minutes later, and No. 9 two minutes later still, just after respiration had stopped. Normal air was then admitted, with recovery.

Henderson as a treatment for wound shock, although on different grounds. The former wishes to excite vigorous respiration by excess of carbon dioxide, in order to pump blood from the abdominal reservoirs; the latter holds that an important factor in shock is the excessive removal of carbon dioxide by the exaggerated respiration due to pain. We have seen that there is no evidence that either of these conditions plays an important part. At the same time, if the respiratory centre has lost in excitability, it does not seem unreasonable to increase lung ventilation by a slight addition of carbon dioxide to the inspired air, so that a more powerful stimulus may be given to the centre. The excess present in the blood would not materially prejudice the amount of oxygen taken up at the alveolar tension, as we have seen on p. 55 above. But, on the other hand, the rebreathing of expired air, which means a defective supply of oxygen, is unquestionably deleterious, and is not to be recommended on any consideration. Haldane is inclined to think that administration of oxygen might be of value in shock. It is not certain, however, that the arterial blood is really insufficiently oxygenated; indeed, the evidence seems to indicate that the trouble does not lie here. What is wrong is that the blood is not supplied to the tissues sufficiently rapidly, owing to the low blood pressure. The more effective treatment is, therefore, to raise this pressure by increasing the volume in circulation.

Fig. 41 (p. 114 above) is of interest in connection with rebreathing, and for the number of the factors involved in the state of shock. A severe muscle

injury caused a progressive fall in the blood pressure, which was exaggerated by massage of the legs in the centre of the tracing. The state was associated with rapid, shallow breathing, and showed no signs of recovery. Three hours and a quarter after the injury, 13·5 c.c. of half-normal lactic acid were injected, with the rather remarkable result of a gradual return of the blood pressure and respiration to normal, which was reached in two hours. Half an hour later, expired air (tube 92 cm. long attached to tracheal canula) was rebreathed for half an hour. The result was a steady fall of blood pressure which reached 60 mm. in about twelve minutes after the tube was removed. The injection of 28 c.c. of gum-saline at this point restored the blood pressure to 100 mm., which lasted until the experiment was stopped about three-quarters of an hour later. We may note that this injection occurred five and a half hours after the injury, and that, so far from "acidosis" being the cause of shock, it apparently cured it, while rebreathing brought it on again.

Local Anæmia.

One of the methods of producing experimental "shock" is that in which the circulation is cut off from a large part of the body for some time. On readmitting the blood to this area, a fall of blood pressure occurs. Whether this procedure is to be regarded as comparable to what happens in wound shock is somewhat doubtful. Indeed, the circumstance that the effect on respiration is that of increase of hydrogen-ion concentration (see Fig. 54) and not the typical one of wound shock suggests

that the state is not the same. But certain facts are instructive. In the tracing of Fig. 52, the abdominal aorta was clamped above the iliacs for an hour. During this time the blood pressure was irregular, but did not fall below 100 mm. On

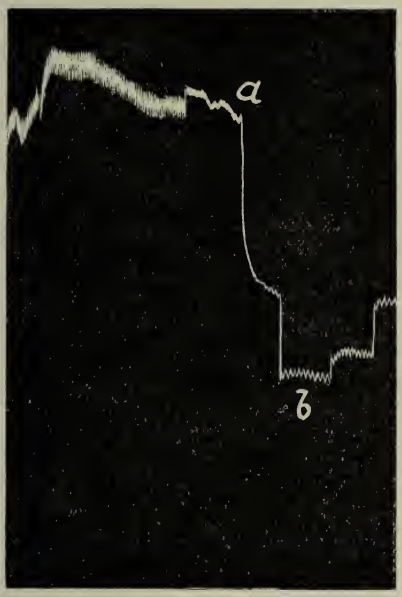


FIG. 52.—Occlusion of Abdominal Aorta.

During the first part of the tracing, the aorta was clipped above the iliacs for an hour.

a. Release of clip. *b*. Ten minutes later.

End of trace—an hour afterwards. No further recovery subsequently.

Bicarbonate reserve—Initial - - - - - 42
On release of clip - - - 32
At end of experiment - - 40

(Cannon and Bayliss.)

releasing the clamp, there was a fall from 124 mm. to 78, which was continued until it reached 56 mm. in about ten minutes. It then commenced to rise and

attained 80 mm. in three-quarters of an hour, but did not rise any further. Now we know from Araki's observations that lactic acid is produced in anæmic areas, so that it is not surprising to find that the bicarbonate reserve was decreased in a sample of blood taken immediately after release of the clamp. But the bicarbonate had returned nearly to its normal value at the end of the experiment, although the blood pressure had not. The conclusion must be that some other factor besides acid was playing a part. It was noticed that, during the compression, there were occasional attacks of dyspnœa, suggesting that some small collateral circulation was going on through the legs and carrying products to the rest of the body. That acid is not the only cause of the fall of pressure in similar experiments is shown by the fact that in another experiment, although the usual fall of pressure occurred on opening the clamp, there was no change in the bicarbonate reserve.

Fig. 53 gives us a further step in the analysis of the phenomena. At *a* the aorta was clamped as in the previous experiments. There was the usual rise of arterial pressure. At *b* the vena cava was clipped, the arterial pressure fell, no doubt owing to diminished inflow into the heart. At *c*, two minutes after the occlusion, the clamp on the aorta was removed. There was a marked fall in blood pressure. At *d* the clip was taken off the vena cava. The arterial pressure partially returned, but not completely. It appears that the fall must have been largely due to the inflow of blood into vessels dilated by the asphyxial products of the tissues,

because there could be very little circulation through the limb with the vena cava clamped. It was a capacity effect, in great part. There were, however, some dilator metabolites which passed into the general circulation, as shown by the more permanent effect. In another experiment, I obtained evidence of dilatation of the intestinal vessels, but it was difficult to be certain that the plethysmograph was not disturbed on removing the clamp. That these dilator substances produced by obstruction of the circulation are, at all events in part, of an acid nature is shown by the respiratory tracing of Fig. 54, which shows an effect like that produced by increase of hydrogen-ion concentration.

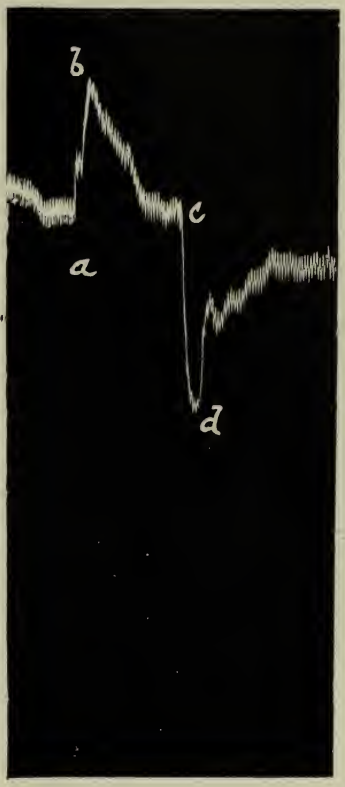


FIG. 53.—**Occlusion of Aorta.**

a. Abdominal aorta clamped.
b. Vena cava clamped.
c. Clamp off aorta.
d. Clamp off vena cava.

From what we have seen already as to the exaggeration of shock effects when combined with hæmorrhage, we expect to find the same effect in these cases. In one such experiment I occluded partially the abdominal aorta above the cœliac axis,

so that the blood pressure below the ligature was kept at about 30 mm. of mercury for thirty-eight minutes. The general blood pressure, which was originally 104 mm., fell, on release of the ligature, to 78 mm., but slowly rose again to 88 mm. in two hours. At this time 16 per cent. of the blood was removed, a quite insignificant amount. It caused, however, a serious and prolonged fall, the pressure being 49 mm. fifteen minutes after the hæmorrhage. In the experiment of which Fig. 55 is a record, we see that the removal of 22 per cent. of the blood had no serious effect during the obstruction of the abdominal aorta. But a marked fall occurred on removal of the clamp. The blood pressure returned practically to its original height in the course of about two hours, but a further hæmorrhage, amounting with the former to 39 per cent., caused a severe fall. As this showed no sign of recovery, gum-saline was given, with complete return to the normal, 123 mm. one hour after the injection.

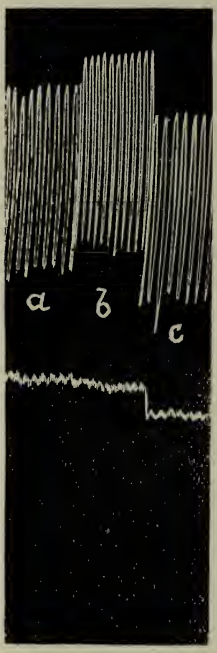


FIG. 54.—**Effect on Respiration of the Products of Tissue Anæmia.**

a. Before release of clamp on aorta.
b. Immediately after removal of clamp.
c. Eleven minutes later.

Injection of Acid (Acidosis).

It was mentioned above that injection of acid occasionally causes a progressive fall of blood pres-

sure, especially if combined with a slight loss of blood. Figs. 21 and 23 illustrate this fact, while the latter figure shows that the injection of bicarbonate solution does not restore the secondary fall. Fig. 56 shows that gum-saline, without alkali, restores it. Hence the low blood pressure was not

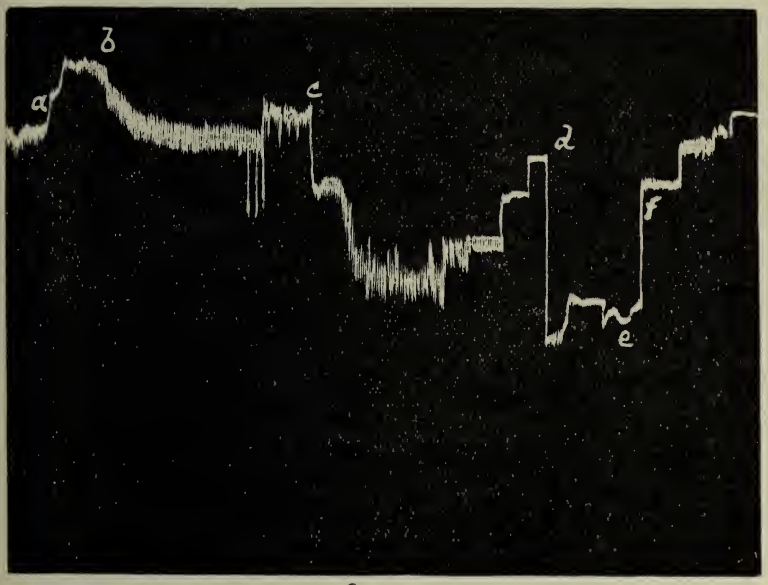


FIG. 55.—**Occlusion of Aorta, Combined with Hæmorrhage. Gum given.**

a. Aorta clipped.
b. 22 per cent. blood removed.
c. Released aorta.
d. Bled 17 per cent.
e. Twenty-five minutes later.
f. After 54 c.c. of gum-saline (equal volume to that of blood lost).
End of trace—one hour after gum.

due to the direct effect of increased hydrogen-ion concentration. It is to be noticed also that the

respiration failed, but returned spontaneously when the blood pressure was raised.

Neither gum nor bicarbonate was of value if a low blood pressure had lasted for more than an hour and a half.

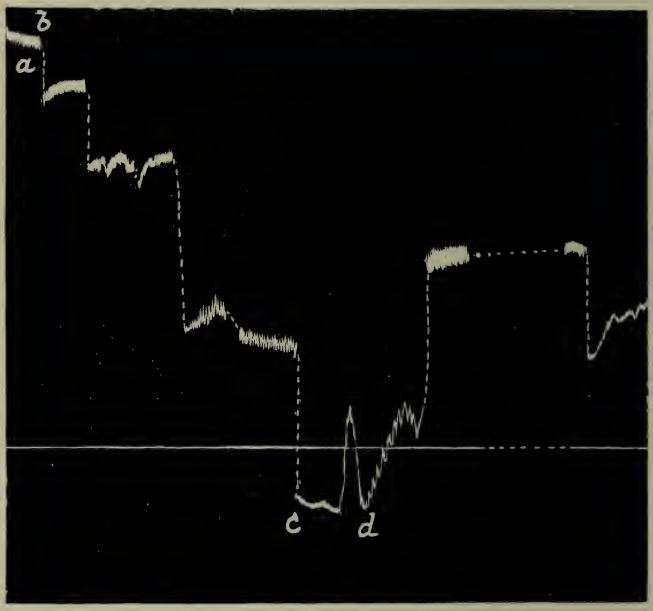


FIG. 56.—**Injection of Acid, followed by slight Hæmorrhage. Effect of Gum.**

a. Blood pressure after 12 per cent. of the blood removed.
b. 17 c.c. half-normal hydrochloric acid given by vein.
c. After two further removals of blood, making 26·5 per cent. altogether. Artificial respiration necessary.
d. Gum-saline, in volume equal to blood removed, injected. Natural respiration restored.
End of tracing—forty minutes after gum.

Injection of Alkali.

Just as acid injections sometimes result in a progressive fall of blood pressure, so may bicarbonate

injections. Fig. 57 shows such a case. The fall was restored by gum-saline, but it is not easy to suggest an explanation of the fact.

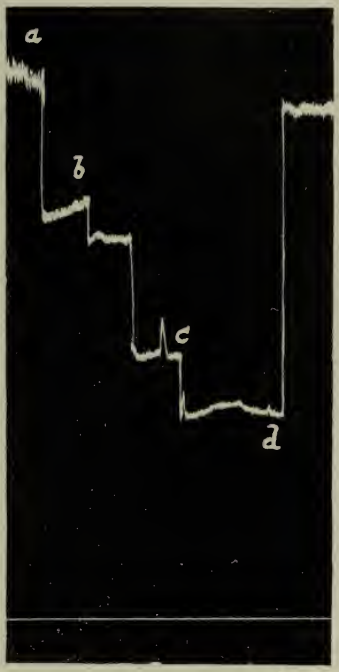


FIG. 57.—Fall of Blood Pressure from Bicarbonate Injection. Effect of Gum.

a. Injection of 4·2 per cent. bicarbonate begun.
b. Injection ended. 17 c.c. in.
c. Half an hour later. Rapid, shallow respiration.
d. 18 c.c. gum-saline. Respiration became normal.

General Vaso-dilatation.

When this state is due to removal of the blood vessels from vaso-motor control, as when the centre is paralysed or the spinal cord cut in the cervical region, intravenous injections have very little, if any, permanent effect (see Fig. 58). It appears as if the blood vessels were able to dilate and so accommodate a large volume of fluid in such states. This view is confirmed by the fact shown in Fig. 58 after *c* and *e*, namely, that the intestinal vessels continue to dilate while the arterial pressure is falling. The arterioles seem to be unable to maintain their "tone" under a raised pressure, unless they are in receipt of vaso-constrictor impulses from the centre. The capillaries may also accommodate an increased volume.

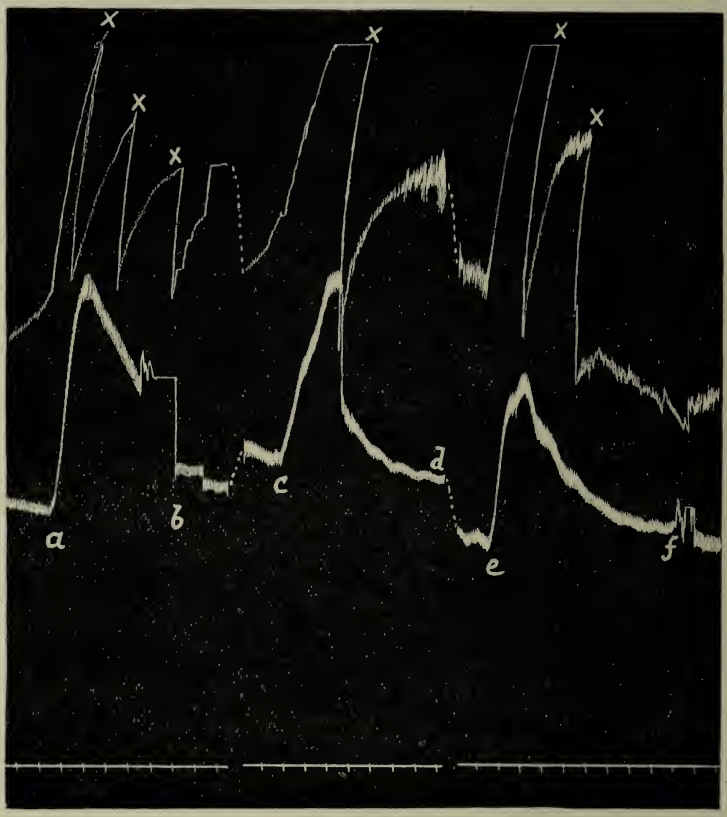


FIG. 58.—**Gum Solution in Spinal Cat.**

Urethane. Cord cut at foramen magnum.
Upper tracing—intestinal plethysmograph.
Lower tracing—blood pressure.

a. 20 c.c. gum.
b. Six minutes later.
c. 20 c.c. gum.
d. Eight minutes later.
e. 20 c.c. gum.
f. Eight minutes later.

End—eighteen minutes after *e*.
Air let out of recorder at X. Time in minutes.

The fluid does not leave the circulation. In one experiment, for example, the blood pressure was 65 mm. of mercury before the injection of gum ; and at this time the corpuscles made up 43 per cent. of the total blood volume. 50 c.c. of gum-saline raised the pressure for a minute or two to 150 mm., but by the time another sample of blood had been taken, it had already fallen to 135 mm. The percentage of corpuscles was reduced by the injection to 32 per cent. Nine minutes later the blood pressure was down to 62 mm. again, but there was no increase in the percentage of corpuscles, so that no fluid had left the blood vessels. Measured by the colorimeter, the blood was diluted in the proportion of 100 to 120 by the gum, and the reading was still 125 when the arterial pressure had returned to its former level.

When the arterial dilatation is due to the action of a drug, such as nitro-glycerin or acetyl-choline, the injection of gum-saline may raise the pressure somewhat, but less than the same amount would do if the blood pressure had been reduced to the same level by hæmorrhage. Experiments on this question are still incomplete.

The Action of Histamine.

The results of Dale and Richards, referred to above, and their suggestion that the products of muscle injury might have a similar effect on the capillaries, indicate that the effect of a gum injection on the "shock" produced by a large dose of histamine, as described by Dale and Laidlaw (1917), would be of interest and importance. The following

experiment will serve to illustrate the result. The blood pressure of a large cat was reduced from 130 mm. to 48 mm. by the slow intravenous injection of 12 mgm. of histamine biphosphate (Dale and Laidlaw produced shock by 10 mgm.). As recovery did not occur in fifteen minutes, 50 c.c. of 6 per cent. gum-saline were run in. The blood pressure rose again to its original level, at which it still remained two hours later. On the view that capillary dilatation and stasis is the cause of the low blood pressure, it seems evident that the raising of the arterial pressure and effective blood volume keeps up the normal circulation until the organism has eliminated the toxic substance (Fig. 59).

On the supposition that stasis in the capillaries would be favoured by arterial constriction, the following experiment was made. A low blood pressure was produced as before by the injection of histamine. The central end of the median nerve was then stimulated. The reflex rise of pressure, however, was not followed by a fall, but remained at a higher level than before the stimulation. Further investigation of this question is desirable.

The fact that 6 per cent. gum-saline is so effective suggests that the concentration of the blood, found by Dale and Laidlaw to take place as a rule in histamine-shock, does not require the gum solution, used when the blood is believed to be concentrated, to be diluted.

A further point of interest is the difference between the effect of gum on the low pressure resulting from arterial dilatation and on that from histamine, a confirmation of the position taken by

Dale and Richards that the point of attack of the dilatation produced by histamine is not the arterioles.

Like other forms of shock, the effect of histamine is accentuated by hæmorrhage. Thus, the removal of 23 per cent. of the blood caused the blood pressure

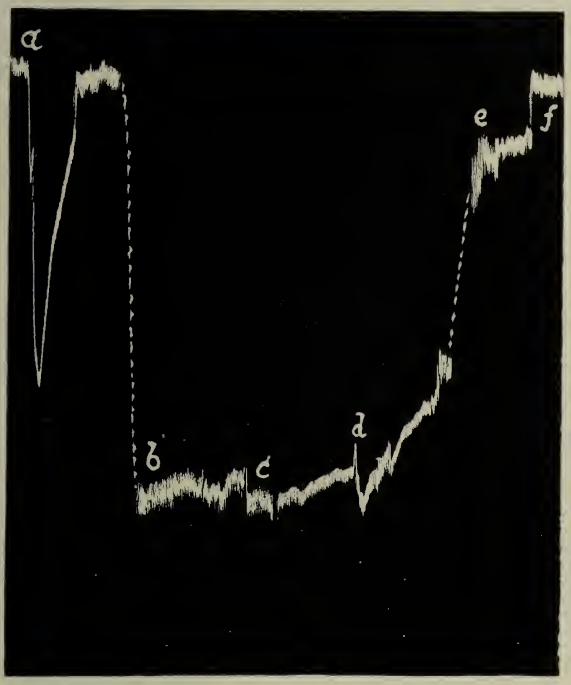


FIG. 59.—Gum in Histamine Shock.

a. Histamine biphosphate, 0·1 mgm. into vein.
b. Height of blood pressure after 5 mgm. histamine.
c. Height after 11 mgm.
d. Fifteen minutes after histamine injection. 50 c.c. gum-saline given.
e. Ten minutes after gum.
f. Two hours and a quarter after gum.

to fall further without recovery, after its reduction by a large dose of the drug. And, by injection of

gum half an hour after the drug had been given, the pressure was not completely restored until about an hour had elapsed.

It should be pointed out that it is naturally impossible to be sure that the blood pressure might not, sooner or later, have recovered spontaneously in these experiments. But we know that, if allowed to remain at a low level for any notable length of time, the nerve centres are paralysed, and the possibility of recovery absent. What may safely be said is that the effect of gum is to remove the eventuality of such an issue.

Gas Infection.

It has been often remarked that a good circulation is of much importance in checking the spread of gas gangrene, as would naturally be expected from the anaerobic nature of the organisms responsible for it.

This being so, favourable results should be obtained by the use of gum injections when the stage of low blood pressure has come on. Fraser and Cowell (1917, p. 20, case No. 7) report a case of gas gangrene of the thigh, where there were no signs of hæmorrhage nor of "shock," although the blood pressure was only 70 mm. An injection of 20 oz. of gum-saline raised it to 110 mm., where it remained until recovery took place. Nos. 8 and 24 of Fraser and Cowell's list are also interesting. Both of these were compound fractures of the femur, with bad gas gangrene, but ultimate recovery. It is not to be understood that gum is put forward as a remedy for this infection, but merely that, if the

blood pressure is low, the patient is placed in a better position for combating the disease if an intravenous injection is given to improve the circulation. The infection is always serious, and, in Fraser and Cowell's list of cases in which gum was used, we may note that there were nine of bad gas gangrene, of which four recovered. Of the sixteen cases in which it was less severe, twelve recovered.

The fact that both the species of *bacillus* (*perfringens* and *sporogenes*) associated with gas gangrene produce acids in their growth, as shown definitely by Wolf and Telfer (1917), shows that the administration of alkaline solutions is not unreasonable. At the same time, as the experimental results with lactic acid described above (p. 69) show, it is probable that raising the blood pressure by means of gum-saline would be at least as effective in removing them by oxidation as their neutralisation after production would be, while the other good effects of a higher blood pressure would be gained. We know that the toxic effects of the infection are due to a specific agent, not to the acids themselves. Moreover, the spread of the disease is retarded by a good supply of oxygen. Hence it would be perfectly justifiable to take up the position that the administration of alkali is to be deprecated, on the ground that it removes the stimulus to the respiratory centre provided by the slight increase of hydrogen-ion concentration, which is not serious in itself, as we have seen above.

It has been noticed by Drummond and Taylor (1918, 2) that the onset of gas infection is marked

by a rise in arterial pressure. This is, no doubt, due to stimulation of the vaso-motor centre by the acid products. The fact has its serious aspect in that, as Major McNee has pointed out to me, a false impression may be given of the state of a patient. The condition of wound shock being one of low blood pressure, owing to deficiency of blood in circulation, the need is for more fluid. The tissues are suffering from anæmia. Now, suppose that there is a rise of pressure owing to the onset of infection and stimulation of the vaso-motor centre. The rise of pressure being caused by constriction of arterioles, the blood supply to the tissues is still further decreased and the production of capillary stasis favoured. It would appear in such cases that benefit might possibly be derived from the combination of a drug which dilates arterioles without depressing the heart, if such a one exists, with the intravenous injection of gum. We should thus assist in the removal of the toxic products in addition to retarding the spread of the infection by more copious supply of blood to the area infected.

Another point is suggested by these considerations to which attention should be directed. As Wiggers (1918) has shown, a dangerous state of shock may exist with a normal arterial pressure, although the form of the pulse wave shows grave disturbance in the circulation. Hence blood pressure readings alone are not to be relied upon as an infallible guide, apart from other indications. Our eyes must be open to the fact that a high blood pressure, if produced by vaso-constriction, is not necessarily indicative of a satisfactory condition.

There is a high blood pressure in the first stage of asphyxia. On the whole, it is safe to take a low blood pressure as a serious sign, while a high blood pressure in the wounded man must be kept under careful observation.

Pulmonary Irritant Gases.

After severe gassing with such agents as chlorine, phosgene, and so on, there frequently occurs a state of collapse, in which the face is grey and signs of low blood pressure show themselves. This is usually preceded by the stage of asphyxial excitation, but it may, apparently, come on very rapidly. In both, of course, there is cyanosis in the sense of want of oxygen; but in the excitatory stage there is violent dyspnœa with raised venous pressure, while in the collapsed state the blood pressure is low and the nerve centres on the way to paralysis and death. In some experiments which I made with cats exposed to chlorine under urethane there was always a fall of blood pressure, and an injection of gum did certainly improve their general condition, although it did not appear that any permanent good was effected.

It seems possible, nevertheless, that some benefit might be afforded by intravenous injections of gum in collapsed cases less severely gassed than my cats were. Some substance might also be found that would retard escape from the pulmonary vessels. Boycott (1918) found that calcium salts were useless in goats. Perhaps concentrated gum would be worth some investigation. Meek and Gasser (1918) found that an animal under ether

might have its blood made to contain 10 per cent. of gum without harm, whilst intact animals had their blood made up to 4 per cent. with no unfavourable symptoms, and a 20 per cent. solution could be injected. Four per cent. in gum would increase the colloidal osmotic pressure to 160 per cent. of its normal value, thus retarding the escape of fluid from the vessels. It would seem worth while to test experimentally the effects of strong gum solutions in œdema of the lungs after poison-gases. The cats referred to above did not show any obvious retardation of the onset of œdema as a result of the injection of 6 per cent. solutions, but these were probably not concentrated enough. If a 20 per cent. solution were used, a man would need about 870 c.c. to make his blood 4 per cent. in gum.

All that we know of the effect of diluting the blood on the production of œdema indicates that saline injections are most likely to be pernicious, although they have been recommended, and statements have been made that the œdema of the lungs was not increased in dogs by their use. If the blood becomes concentrated at later stages after gassing, it would be reasonable to restore it to its normal dilution, provided that the risk of œdema of the lungs were satisfactorily excluded.

In Conclusion, to sum up the data of the preceding pages, we may say that gum has shown itself to be useful in cases of low blood pressure produced by a great variety of causes. Erlanger (Report of American Shock Committee) has recently confirmed the results of my experiments, and says that gum acacia "holds the plasma in the vessels

in all forms of shock," that is, as produced experimentally.

Illustrative Cases.

Several cases of the use of gum solutions in wounded men have been quoted already. I may add a few more as being instructive in regard to the variety of the conditions treated.

Cowell (1917, p. 63) gives a case of severe abdominal shell wound. Arrival at Casualty Clearing Station about an hour afterwards. Pale, hands and feet cold, although the day was warm. Blood pressure—82 mm. At operation, ten rents in the intestine were repaired, and, after intravenous infusion of gum-saline, a good recovery was made.

Fraser and Cowell (1917, p. 20). No. 5. Compound fracture of femur. Shock severe, hæmorrhage moderate. Blood pressure—50 mm. Raised to 125 mm. by 20 oz. of gum-saline. Recovery.

No. 6. Torn femoral vein. Much loss of blood. Blood pressure raised from 90 mm. to 100 mm. by 15 oz. of gum-saline. Recovery.

No. 10. Compound fracture of tibia. Amputation. Moderate shock, hæmorrhage and gas gangrene. Blood pressure raised by gum from 70 mm. to 120 mm. Recovery.

No. 22. Multiple wounds. Raised from 95 mm. to 130 mm. Recovery.

No. 27. Abdominal wound. Both shock and hæmorrhage severe. Blood pressure raised from 45 mm. to 80 mm. by 30 oz. of gum-saline. Subsequently rose to 120 and 140 mm. Recovery.

Drummond and Taylor (1918). No. 7. Com-

pound fracture of femur, with severe laceration of muscles. Blood pressure—80 mm. Gum before operation raised pressure to 128, but fell during operation to 88 mm. Two and a half hours later more gum was given, raising the pressure to 120. It rose further, and was 152 eighteen hours later. Recovery.

No. 10. Severe injury to scalp. Shell wounds of left leg and arm. Blood pressure—116, but signs of shock. Pressure fell to 72 mm. during operation. Gum given raised it to 112 mm., and it had risen to 120 mm. twenty-three hours later. Recovery.

No. 14. Wounds of knee-joint. Rupture of popliteal artery. Blood pressure—128 mm., but fell to 86 mm. during operation. Gum given nine and a half hours later raised it to 150 mm., and maintained it at 132 mm. Recovery.

No. 19. Compound fracture of femur. Shell wounds of buttock, chest wall, and thigh. Blood pressure—120, but fell to 80 mm. during operation. Gum solution raised it to 118 mm. permanently. Recovery.

No. 20. Double compound fracture of tibia and fibula. Blood pressure—76 mm. Raised to 122 mm. by gum, but fell again to 92 mm. during double amputation. Recovery.

No. 22. Compound fracture of tibia and fibula. Gas gangrene. Blood pressure—128 mm. at beginning of operation (amputation under spinal anæsthesia), but fell to 64 mm. Gum solution then raised it to 110 mm. permanently. Recovery.

No. 30. Compound fracture of femur. Shell wounds of left arm and foot. Blood pressure—45

mm. Raised by gum to 110 mm., falling to 90 mm. during operation, but rose to 120 mm. in twenty hours. Developed gas gangrene and died later.

No. 34. Shell wound of abdomen and cervical spines. Blood pressure—124 mm., falling to 68 mm. during operation. Gum raised it to 100 mm., and it was 120 mm. twenty hours later. Died of "shock" twenty-four hours after operation.

Historical.

The reader will probably be interested in the fact that, according to Spratt's "History of the Royal Society," published in 1667, it was Christopher Wren who was "the first Author of the Noble Anatomical Experiment of Injecting Liquors into the Veins of Animals." The passage continues (I quote from the third edition, p. 317)—"An Experiment now vulgarly known; but long since exhibited to the Meetings at Oxford, and thence carried by some Germans, and published abroad. By this operation divers Creatures were immediately purg'd, vomited, intoxicated, kill'd or revived, according to the quality of the Liquor injected. Hence arose many new Experiments, and chiefly that of Transfusing Blood, which the Society has prosecuted in sundry instances, that will probably end in extraordinary Success."

More details of the experiments will be found on p. 128 of the first volume of the *Philosophical Transactions* (1665-1666), where complaint is made that in "books printed beyond the seas" the origin of the method is ascribed to others than the "true Inventor." From this account, and

that given by Boyle in his "Usefulness of Experimental Philosophy" (2nd Part, 1671), it appears that the idea was due to Wren. He suggested the experiments to Boyle, who had the apparatus (a quill attached to a syringe) made. Wren then performed the experiments before some of the Oxford meetings of the Royal Society, which were held at that time in the Warden's lodgings at Wadham College. In the "Works" of Boyle, published in 1772, the description will be found in Vol. 2, Part 2, Essay 2, pp. 88 and 89 (called "Postscript"). Opium was the first material tested, and found to have its characteristic effect.

The transfusion of blood from one dog to another was done by Dr Lower (*Phil. Trans.*, I, p. 353), and gave rise to some remarkable suggestions on Boyle's part, such as the possibility of transference of the mental qualities of one dog to another.

I may venture to call attention to a curious modern parallel to some statements made in the above quotations. In November 1916 a paper by the present author was read before the Royal Society. In this paper a solution of gum arabic in physiological saline was recommended to raise the blood pressure, as has been discussed in the preceding pages. In May of the present year (1918) our Shock Committee received a copy of a circular issued to German Field Hospitals. The writer says that salt solution with adrenaline, and also transfusion of blood, have been found disappointing. He therefore draws attention to "a method which was brought to his notice by Conradi, and which originated with the physiologist, Kestner, who,

from certain theoretical considerations, was led to try a solution of gum arabic in physiological saline." He states that, with the most cautious interpretation of results, the conclusion has been come to that they are better than those hitherto obtained with other methods of replacing blood.

Comment is scarcely necessary.

Dangers of Raising the Blood Pressure.

It is obvious that when either blood transfusion or gum injection is practised, there is some risk of the starting afresh of hæmorrhage which may have ceased owing to the fall of blood pressure.

In the case of severely lacerated limbs, Drummond and Taylor (1918, p. 4) have found it best to apply a tourniquet before transfusion is begun, and to deal with the bleeding points at the subsequent operation. Case No. 20, referred to briefly above, illustrates their procedure: Admitted two hours and a quarter after being wounded in both legs by rifle grenade. Very pale and restless. No pulse to be felt in radial. Systolic blood pressure—76 mm. The right leg was blown off in the middle third. The left leg showed severe compound fracture of the tibia and fibula in the middle third, with mutilation of the ankle-joint and tarsus. Hæmorrhage still proceeding. Tourniquet applied round each thigh and transfusion with gum-saline begun at once. Blood pressure raised to 122 mm., and patient obviously much better. Double amputation performed, leading to a fall in blood pressure to 92 mm. Twelve hours later the pressure was 104 mm. and a good recovery was made.

The stoppage of the circulation in a part, as we have seen, usually leads to a fall of blood pressure on release of the obstruction. But this fall is transitory, and the tourniquet would naturally not be released as rapidly as the removal of the clip in the experimental cases. The fall of pressure would also be counteracted by the previous injection of gum, made possible by the arrest of the hæmorrhage.

In the case of intra-abdominal bleeding, it may be necessary not to start the transfusion until the operation is begun, finding the sources of the hæmorrhage as soon as the abdomen is opened. Although this may entail a regrettable delay, there seems to be no alternative.

Primary shock, as pointed out by Captain Kenneth Walker, is of benefit in stopping hæmorrhage. Clots may then form and the vessels contract up. At any rate, the risk of starting renewed bleeding is not sufficiently great to prevent a procedure that may save a man's life.

There is one point to which, as far as I know, attention has not been particularly directed. When oxygen inhalation was first used in asphyxia from pulmonary irritant gases, its use was, for a time, retarded on account of the objection made by patients to its effects. Haldane has pointed out that, when the nerve centres have become more or less paralysed by want of oxygen, the patient may be quiet and feeling fairly comfortable. But this state is very dangerous, and death not far away. The first result of inhalation of oxygen is to awaken the dormant sensibility of the nervous system, so

that the misery of the state is again appreciated. It is natural that the patient should oppose what seems to him to have made him worse. Persistence in the use of oxygen, however, sooner or later removes the unpleasant effects, and may save an otherwise doomed life. Similarly, a prolonged state of shock with low blood pressure leads to depressed excitability of the nerve centres, and the first effect of raising the pressure by blood or gum solution is to arouse sensibility to the pain and discomfort of the wounded state. Moreover, the process of recovery in the centres themselves is probably associated with unpleasant sensations. It seems likely, then, that it might hastily be assumed that harm was being done, when the effects observed were merely due to the returning of the necessary activity in the brain.

Slowness of Recovery.

If the nerve centres have suffered much from prolonged anæmia, they require some time to recover, although this may ultimately take place. The way in which this circumstance shows itself is a more or less gradual rise in the blood pressure after the injection of gum is ended.

It occasionally happens that a fairly rapid increase in blood pressure is followed, half an hour or an hour later, by some degree of temporary fall, or, as Cannon has noticed in wounded men, an attack of "shivering and blueness." This passes off and is no cause for alarm. It has been suggested that it may be due to some disturbance in the "colloidal equilibrium" of the blood. I have seen sometimes a fall of blood

pressure in the cat to result from a reinjection of its own blood. There is, of course, a colloidal change in blood as soon as it leaves the blood vessels. On the other hand, the "shivering and blueness" may be an aspect of the process of recovery of the bulbar centres.

General Conclusion.

In attempting to frame some conception of the *nature of wound shock*, so far as is possible from the data at hand, we arrive at something of this kind. Various causes in combination, some nervous, some chemical, each associated with a reduction of arterial pressure, and all exaggerated by hæmorrhage, result in a state of collapse, whose symptoms seem to be sufficiently accounted for by the effects of a more or less prolonged low blood pressure. Along with hæmorrhage, the most serious of these collateral causes is the absorption of toxic products from injured tissues, especially muscle. These products appear to have a dilator action on the capillaries, an action allied to that of histamine; blood is hereby withdrawn from circulation and held up by stasis. This condition tends to become worse and worse, unless the continuous inflow of the toxic products is counteracted. The injured parts should, therefore, be removed as soon as possible; and this is an additional argument for operative treatment at the earliest opportunity. The toxic products already absorbed may be eliminated or destroyed if the blood pressure and volume of blood in circulation be raised by appropriate intravenous injection. If, however, the low

blood pressure has lasted more than a certain time, which depends on the degree of anæmia, the nerve centres become paralysed. In its early stages this paralysis may be recovered from, if means are taken to improve the circulation as quickly as possible. After a longer period of anæmia, no recovery is possible by any method yet devised, and Mott (1918) has found structural changes in the nerve cells at this stage. In practice, the advent of the irrecoverable stage cannot be known until intravenous injection has been tried and failed. As already pointed out, this may be regarded as an advantage in the use of gum rather than blood, since there can be no reason to be economical in its use.

Brief Recommendation as to the Practical Use of Gum Solutions.

The most important factor in the *treatment* of wound shock is, then, the ensuring of an adequate supply of blood (that is, of oxygen) to vital organs, especially to the nerve centres.

This is most easily done by the intravenous injection of a 6 per cent. solution of gum acacia in 0·9 per cent. sodium chloride, in order to increase the volume of blood in circulation and to raise the arterial pressure. It is possible that there may be cases in which gum is less effective than transfusion of blood or injection of preserved blood corpuscles; but, so far as definite evidence goes, the difference does not seem to amount to much. If there has been a very large loss of blood, it is reasonable to make use of blood itself, but it may effectively be supplemented by gum, and economy in blood attained.

McNee's experience (1918) has been that gum is as good as blood, and that what is really needed is an increase in the total volume of fluid in circulation

The injection, one pint to begin with, should be given as early as possible after the injury, if any sign of wound shock begins to appear. There is no need to economise in the use of gum solution, and delay, with the view of giving opportunity for spontaneous recovery, may be dangerous.

If only partial benefit is obtained in half an hour or so, a further injection may be made. If there is no benefit in half an hour, blood of preserved corpuscles may be used, if available. Otherwise, a further gum injection may safely be tried. It is probable that it will be found unnecessary to use blood in the majority of cases.

A gum injection before, during, or after an operation is frequently valuable, if the blood pressure is low or tends to fall.

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